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Original Article

Passive leg raising tests under a monitoring device to predict fluid responsiveness in off-pump coronary artery bypass grafting patients

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Abstract: The debate concerning the surgical prognosis of passive leg raising tests with a supine position (PLRSUPINE) under the MostCare/PRAM continuous non-invasive cardiac output monitoring system in the preoperative period of off-pump coronary artery bypass grafting (OPCABG) remains open. The present study aimed to investigate volume responsiveness, diagnostic cut-off values, and safety levels of PLRSUPINE in OPCABG patients. Hemodynamic data of 80 OPCABG patients with 156 times of PLRSUPINE was recorded using the MostCare/PRAM device. Of these, 85 PLRSUPINE instances were verified by volume expansion (VE) tests (250 mL colloid infusion in 15 minutes). According to results, VE yielded 59 positive results and 26 negative consequences. Mean percentage increases of stroke volume (SV) in VE, 85 verified PLRSUPINE, and 156 PLRSUPINE were 24.7±25.4%, 20.0±19.7, and 23.0±25.3%, respectively. The diagnostic cutoff value of increased SV in VE tests of 250 mL colloid infusion in 15 minutes was 12-14% of fluid responsiveness. PLRSUPINE under the MostCare/PRAM device is suitable for prediction of fluid responsiveness in the preoperative period of OPCABG. Diagnostic efficacy of stroke volume variation (SVV) and pulse pressure variation (PPV) was much lower than that of PLRSUPINE, with cut-off values of 9.2% in SVV and 11.2% in PPV. In conclusion, in the preoperative period of OPCABG, PLRSUPINE may cause lower efficacy in fluid responsiveness than VE testing with 250 mL colloid infusion in 15 minutes.

Keywords: Off-pump coronary artery bypass grafting, passive leg raising test, fluid responsiveness, stroke volume variation, pulse pressure variation

Introduction

The concept of maintaining an ideal hemodynamic state in the preoperative period was initially put forward by Shoemaker in 1988. Since that point, the aim of maintaining the optimal cardiac preload has been the focus of fluid therapy in the preoperative period [1]. In addition, determining the optimal fluctuating load state for patients is a major key for liquid therapy. A reversible endogenous fluid challenge, passive leg raising testing (PLR) is safer, simpler, and widely applied [2, 3]. Furthermore, results of this test remain completely reliable, even in conscious patients or those with cardiac arrhythmias. Built on the above advantages, current studies mainly focus on PLR, the most promising method for prediction of fluid responsiveness [4-6]. Under normal physiological conditions, PLR may recruit approximately 300 mL of intravascular volume [7]. In a study performed by Godfrey SV in 11 health volunteers, PLR was measured by transatlantic echocardiography [8]. Results indicated that the mean percentage difference of SV (D-SV) induced by PLR was 5.7% (P=0.16). Moreover, 45% of the volunteers had a mean percentage change over 10%, with 19.1% as the maximum. Therefore, hemodynamic changes caused by PLR are complicated. Future studies are necessary to explore diagnostic cut-off values of PLR, improving prediction of fluid responsiveness in patients with hypovolemia.

Furthermore, in the postoperative period of cardiac surgeries, fluid therapy becomes even more complex and difficult. This is due to severe underlying diseases, cardiopulmonary dysfunction, other possible organ dysfunctions, injuries after extra corporeal circulation, prolonged operations, anesthesia duration, significant surgical stress, and trauma [9, 10]. Therefore, a hemodynamic monitoring device, the MOSTCARE/PRAM continuous non-invasive cardiac output monitoring system, was utilized to measure real-time cardiac output and SV variation during PLR. The present study was designed to explore diagnostic efficacy, cut-off values, and safety levels of PLR testing under the MOSTCARE/PRAM device for prediction of fluid responsiveness.

Materials and methods

Patients

A total of 80 patients undergoing off-pump coronary artery bypass grafting (OPCABG) in Beijing Anzhen Hospital, between October 2016 and January 2017, were recruited. This prospective cohort study was approved by the Medical Ethics Committee of Anzhen Hospital. Informed consent was obtained from all patients or family members.

Patients that underwent OPCABG met the inclusion criteria. Exclusion criteria: Patients aged below 18 or above 80; BMI below 15 kg/m^2; Patients with intra-abdominal hypertension, such as abdominal compartment syndrome; Patients with pulmonic valve disease or aortic valve disease; Patients with mitral stenosis or mild and severe mitral insufficiency; Patients with an intracardiac shunt; Patients with deep venous thrombosis of the lower extremities; Patients with counterindications of leg raising, such as osteonecrosis of the femoral head, fractures, and injury of the lower extremities or pelvis.

Methods

All patients underwent general anesthesia, complete sedation, and mechanical ventilation. Real time cardiac output was measured by the MostCare continuous non-invasive cardiac output monitoring system, connected with a radial artery catheter. Central venous pressure was recorded by a central venous catheter. During this process, the lower extremities were not fixed by the elastic bandage. Volume statuses of the patients were closely monitored and fluid responsiveness testing was performed when hypovolemia was suspected. VE refers to the presence of at least one clinical or biological manifestations of hypoperfusion, including a systolic blood pressure lower than 90 mmHg (or a decrease of more than 50 mmHg in hypertensive patients), urine output below 0.5 mL/kg per hour for at least two hours, tachycardia (heart rate >100 bpm), and the presence of skin mottling.

Fluid responsiveness tests include PLR and volume expansion. In paired fluid responsiveness tests, fluid therapy was discontinued, while doses of vasoactive agents and parameters of ventilator remained unaltered. Afterward, monitoring indexes were gathered under the following experimental conditions: Patients maintained the supine position for five minutes; PLR from the supine position (PLRSUPINE); Supine position for five minutes. During PLRSUPINE tests, patients were moved from the supine position to 45 PLR position and maintained for 5 minutes. In VE tests, each patient was rapidly given 250 mL colloidal solution (albumin or dextran) within 15 minutes. An increase of at least 15% of D-SV in VE was defined as progressive. Receiver operating characteristic (ROC) curves for PLR-induced percentage changes in SV were obtained. Thus, discriminating the threshold of responders and non-responders to fluid loading was determined.

Measurements

Cardio output was continuously measured by invasive arterial blood monitoring and pulse contour analysis techniques. Systolic pressure (Sys P.), diastolic pressure (Dia P.), dicrotic pressure (Dic P.), heart rate (HR), cardio output (CO), cardiac index (CI), SV, SV index (SVI), systemic vascular resistance (SVR), systemic vascular resistance index (SVRI), cardiac circulation efficacy (CCO), maximum pressure gradient (dP/dT), SV variation (SVV), and pulse pressure variation (PPV) were recorded every 30 seconds by the MOSTCARE continuous non-invasive cardiac output monitoring system (PRAM; Vytech HealthTM, Padova, Italy). Central venous pressure was obtained using a central venous catheter. Central venous pressure (CVP) was shown at the end of expiration for three consecutive respiratory cycles, with mean values measured.

Statistical analysis

Results are expressed as mean ± SD. All analyzed variables were normally distributed.

Table 1. Characteristics of patients

Characteristic	Patients (n=73)
Age (y)	60.5 (35-78)
Male/female	47/26
Height (cm)	166.2 (149-185)
Weight (kg)	69.1 (45-95)
Diagnosis	
CAD	73
HT	47
DM	30
Vaso-pressive agents	
Dopamine (μg/kg per minute)	3
Ventilator settings	
Tidal volume (ml/kg)	8 ml/kg

Comparisons of hemodynamic variables before and after intervention were assessed using paired Student's t-tests. Linear correlations were tested using the linear regression method. ROC testing was used for diagnostics. Area under ROC curves were compared in all patients using Hanley-McNeil tests. *P<0.05* indicates statistical significance. Statistical analysis was performed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA) for all tests except Hanley-McNeil tests.

Results

Patients

Six patients were excluded for conversion to extracorporeal circulation, restlessness, and cardiac arrhythmias. Therefore, 74 patients treated with OPCABG were included and monitored during and after surgery. Characteristics of the patients are shown in **Table 1**. In this study, PLRSUPINE was performed 156 times, with 85 times verified by VE. VE yielded 59 positive results and 26 negative results. Hemodynamic parameters recorded by MostCare during VE and PLR are shown in **Tables 2** and **3**. Results of paired tests between VE and PLR manoeuvre are shown in **Table 4**.

The blood pressure (BP) of 2 patients decreased significantly after PLR. However, BP levels returned to normal after postural adjustment and vasopressor therapy. The BP of one patient was substantially increased in PLR, but rapidly declined in the following supine position. Therefore, emergent thoracotomy and extra corporeal circulation were performed. Aspiration was not found in this study.

Analysis of fluid responsiveness

Results of the ROC curve of the percentage increases of SV, SVV, and PPV, as well as other parameters, are shown in **Tables 5-7** and **Figure 1**. Using the optimal cut-off value of D-SV in PLRSUPINE verified with VE as the diagnostic criteria, the fluid responsiveness of 156 PLR tests was determined, obtaining 107 responders and 49 non-responders. Results of ROC curves showed, for SVV, the AUC was 0.690 (95% CI 0.600~0.780, *P<0.001*), optimum cut-off value was 9.2%, sensitivity was 66.4%, and specificity was 65.3%. For PPV, the AUC was 0.639 (95% CI 0.600~0.775, *P<0.001*), optimum cut-off value was 11.2%, sensitivity was 62.6%, and specificity was 79.6%.

Analysis of optimum cut-off values in the ROC curve

When the results of VE tests (D-SV >15% as volume responders) were defined as diagnostic criteria, for D-SV in PLRSUPINE, the area under the ROC curve (AUC) was 0.938 (95% CI 0.876~1.000, P<0.001), optimum cut-off value was 10.8%, sensitivity was 94.9%, and specificity was 88.5%. For CVP of VE, the AUC was 0.349 (95% CI 0.225~0.474, P=0.028). For SVV of VE, the AUC was 0.723 (95% CI 0.604~0.842, P=0.001), optimum cut-off value was 4.3%, sensitivity was 88.1%, and specificity was 50%. For PPV of VE, the AUC was 0.744 (95% CI 0.636~0.852, P<0.001), optimum cut-off value was 10.2%, sensitivity was 66.1%, and specificity was 76.9%. For SVV of PLR, the AUC was 0.704 (95% CI 0.578~0.830, P=0.003), optimum cut-off value was 5.0%, sensitivity was 86.4%, and specificity was 53.8%. For PPV of PLR, the AUC was 0.765 (95% CI 0.663~0.868, P<0.001), optimum cut-off value was 10.2%, sensitivity was 62.7%, and specificity was 88.5%.

Discussion

As early as 1965, Thomas and his colleagues found that SV increased in the healthy population but decreased in patients with ischemic heart disease after PLR [11, 12]. Baseline posture includes the 45° semi-recumbent position

Table 2. Hemodynamic parameters of 85 groups of PLRSUPINE and volume expansion recorded by MOSTCARE

	PLR-Baseline	PLR-Max	PLR-D (%)	VE-Baseline	VE-Max	VE-D (%)
CVP	7.1±2.5			7.1±2.5		
SVV	10.1±7.2	17.9±10.7	135.0±181.3	9.6±7.3	20.4±11.1	194.2±244.3
PPV	12.3±9.2	19.2±12.8	97.0±173.4	12.7±9.5	22.6±13.0	145.2±208.9
Dia P.	58.5±7.7	63.5±8.8	9.3±7.1	58.4±9.4	131.6±22.4	11.3±10.4
Sys P.	117.2±17.9	129.6±20.0	10.8±8.5	117.0±19.9	78.7±15.3	14.1±12.3
Dic P.	70.5±14.8	77.2±14.4	10.3±8.7	69.7±14.4	89.0±17.0	14.2±12.6
HR	82.9±16.6	86.8±16.2	5.1±7.1	82.9±15.1	60.8±19.1	6.7±10.9
SV	50.7±16.9	63.5±8.8	20.0±19.7	50.5±14.3	61.9±18.5	24.7±25.4

Note: B stands for the mean value of parameters two minutes before PLR; Max stands for the maximum value after PLR; D stands for the percentage increase of parameters between maximum value after PLR and baseline value two minutes before PLR, similarly hereinafter.

Table 3. Results of paired tests between PLRSUPINE and VE

Variables	Paired test between fluid administration and PLRSUPINE		
	Paired difference	t/Z	*P* (two-tailed)
D2-SV & D1-SV	-0.047	-2.783*	0.005
B2-Dia P. & B1-Dia P.	0.031	0.047	0.963
B2-Sys P. & B1-Sys P.	0.192	0.116	0.908
B2-Dic P. & B1-Dic P.	0.792	0.664	0.508
B2-HR & B1-HR	-0.013	-.268*	0.789
B2-SVRI & B1-SVRI	-41.218	-.377*	0.706
B2-CCE & B1-CCE	40.888	-.475*	0.635
B2-CI & B1-CI	-0.020	-0.483	0.63
B2-SVI & B1-SVI	-0.009	-0.015	0.988
B2-CO & B1-CO	22.069	1	0.32
B2-SVV & B1-SVV	0.443	-.682*	0.495
B2-Dp/Dt & B1-Dp/Dt	0.019	0.759	0.45
B2-PPV & B1-PPV	-0.438	-.923*	0.356
B2-SVR & B1-SVR	-24.497	-.305*	0.76
B2-SV & B1-SV	0.169	0.173	0.863

Note: *stands for Wilcoxon test; 1 stands for PLRSUPINE, 2 for VE, similarly hereinafter.

(PLRSEMIREC) or from the supine position (PLRSUPINE). Compared with PLRSEMIREC, PLRSUPINE may have a lower hemodynamic impact. Thus, it should not recruit the blood of the splanchnic reservoir. However, PLRSUPINE could be considered as an alternative to PLRSEMIREC in some conditions, including increased abdominal pressure, in which PLRSEMIREC can be contraindication. In a study containing 35 patients with circulatory failure, the effects of PLRSEMIREC on the cardiac index were reached when 312 (250-350) mL of saline was injected [13]. For OPCABG patients, it might be a disaster to get outdated volume expansion tests of 500 mL solution in 10 minutes.

Regarding D-SV in 85 cases of VE, 85 paired PLRSUPINE and 156 PLRSUPINE was 24.7±25.4%, 20.0±19.7, and 23.0±25.3%, respectively. There were no significant differences between baseline SV, SVRI, HR, SVV, and PPV between VE tests and paired PLR tests. The SV increase value of PLRSUPINE was 4.7% less than VE tests, with a *p*-value of 0.035, indicating the efficacy of PLRSUPINE in OPCABG patients was lower than that of 250 mL glial solution in VE tests. For the D-SV in PLRSUPINE, the AUC of volume responsiveness was 0.938. Considering the risk of hypovolemic shock induced by significant decreases of BP in PLRSEMIREC when the patient's head was raised, along with the danger of acute right ventricular volume overload caused by complete PLR, it was argued that PLRSUPINE is more suitable and safer for fluid responsiveness tests than PLRSEMIREC under the MostCare/PRAM device in the postoperative period of cardiac surgery.

It has been generally accepted that an SV increase of 10% or less in fluid therapy has already reached to normal blood pressure or optimal blood volume. Thus, no further VE is needed [8]. In addition, a prospective controlled trial of critically ill patients at a European center found that, compared with echocardiography, the error rate for CO measured by the MostCare device was 27.3% [14]. Ex-

Table 4. Hemodynamic parameters of 156 times PLRSUPINE recorded by MOSTCARE

	PLR-Baseline	PLR-Max	PLR-D (%)
CVP	7.14±2.45		7.67±2.4524
Dia Pmax	60.04±9.46	66.85±11.91	11.78±11.48
Sys P.	118.71±20.58	134.17±25.15	13.38±12.44
Dic P.	73.63±15.80	82.83±18.36	12.97±13.32
HR	80.81±19.64	84.72±19.82	5.23±7.85
SVRI	2558.08±607.39	2875.84±684.11	13.34±14.37
CCE	22.36±278.22	23.09±285.81	-46.42±388.91
CI	2.35±0.61	2.86±1.00	21.51±26.55
SVI	31.42±12.06	38.27±15.00	22.98±25.44
SVV	10.92±7.29	18.81±10.33	124.41±182.69
Dp/Dt	0.92±0.31	1.15±0.57	25.91±45.07
PPV	13.12±9.24	20.89±12.99	106.37±187.23
SVR	1438.01±303.09	1614.36±336.04	13.23±14.32
CO	16.19±150.07	17.41±154.13	21.57±26.46
SV	55.35±21.23	67.41±26.69	23.02±25.28

Table 5. Area under the curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
cvp	.349	.064	.028	.225	.474
D1-Dia Pmax	.556	.065	.409	.430	.683
D1-Sys P.	.559	.066	.391	.430	.687
D1-Dic P.	.580	.064	.241	.454	.706
D1-CI	.759	.055	.000	.651	.867
D1-SVI	.829	.051	.000	.729	.930
D1-SVV	.453	.067	.489	.322	.584
D1-PPV	.432	.064	.321	.307	.557
D1-CO	.771	.055	.000	.664	.878
D1-SV	.938	.031	.000	.876	1.000
A1-SVV	.704	.064	.003	.578	.830
A1-PPV	.765	.052	.000	.663	.868
A4-SVV	.723	.061	.001	.604	.842
A4-PPV	.744	.055	.000	.636	.852

Test results variable(s): cvp, D1-Dia Pmax, D1-Dic P., D1-SVI, D1-SVV, A1-SVV, A4-SVV, A4-PPV has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. a. Under the nonparametric assumption. b. Null hypothesis: true area =0.5.

amining this error rate, D-SV of VE defined as diagnostic criteria of VE, which ranged from 11% to 19%. Taking the D-SV of 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, and 19% as diagnostic criteria of VE, ROC analysis showed the AUC of PLR in volume responsiveness was 0.907, 0.938, 0.938, 0.942, 0.885, 0.938, 0.813, 0.813, and 0.800, respectively. PLR, a reversible endogenous fluid challenge, was thought to be the most promising method of predicting fluid responsiveness [15-17]. Present results suggest that the diagnostic cutoff value of increased SV in VE tests of 250 mL colloid infusion in 15 minutes is 12-14% in fluid responsiveness in the preoperative period of OPCABG.

Hemodynamic changes induced by PLR are transient [18-20]. Therefore, a method that could measure SV quickly should be utilized. Pulmonary artery thermodilution, partial CO_2 rebreathing, PiCCO, arterial pressure waveform analysis (such as Vigileo/FloTrac system), and echocardiography have been widely used techniques in PLR-related research. Their predictions for fluid responsiveness are very consistent, with AUC values generally above 0.900 [21-23]. The MostCare continuous non-invasive cardiac output monitoring system was more precise, with a high sampling frequency of 1000 Hz (different from 100 Hz adopted in further pulse contour analyses) [24, 25]. It may measure SV and CO in one cardiac cycle without calibration or pre-adjustment [26, 27]. Studies have shown that measurements of CO and its substitutes by the MOSTCARE device were highly consistent with the results of golden standards, such as pulmonary artery thermodilution and echocardiography [28].

In the current study, SV and its substitutes were measured every 30 seconds. Results showed that SV started to increase at 1.0 minute after leg raising in 156 PLR from the supine position, with the peak appearing in 2.6±1.5 minutes. Therefore, it could be maintained that the prompt and transient hemodynamic effects induced by PLR could be detected by MostCare in time in a timely and accurate manner. The degree of hemodynamic changes caused by PLR was correlated with cardiac preload and the volume status of the abdomen and lower extremities. Capacitance

Table 6. ROC analysis of PLR-related parameters

Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
CVP	0.349	0.064	0.028	0.225	0.474
D1-SV	0.938	0.031	0.000	0.876	1.000
D1-Dia Pmax	0.556	0.065	0.409	0.430	0.683
D1-Sys P.	0.559	0.066	0.391	0.430	0.687
D1-Dic P.	0.580	0.064	0.241	0.454	0.706
D1-SVV	0.453	0.067	0.489	0.322	0.584
D1-PPV	0.432	0.064	0.321	0.307	0.557
A1-SVV	0.704	0.064	0.003	0.578	0.830
A1-PPV	0.765	0.052	0.000	0.663	0.868
A2-SVV	0.723	0.061	0.001	0.604	0.842
A2-PPV	0.744	0.055	0.000	0.636	0.852

a. Under the nonparametric assumption. b. Null hypothesis: true area =0.5.

Table 7. ROC analysis of PLR-related parameters

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.907	.040	.000	.828	.987
.938	.034	.000	.870	1.000
.938	.031	.000	.876	1.000
.942	.033	.000	.878	1.000
.885	.045	.000	.796	.975
.938	.031	.000	.876	1.000
.813	.051	.000	.714	.912
.813	.051	.000	.714	.912
.800	.051	.000	.700	.901

a. Under the nonparametric assumption. b. Null hypothesis: true area =0.5.

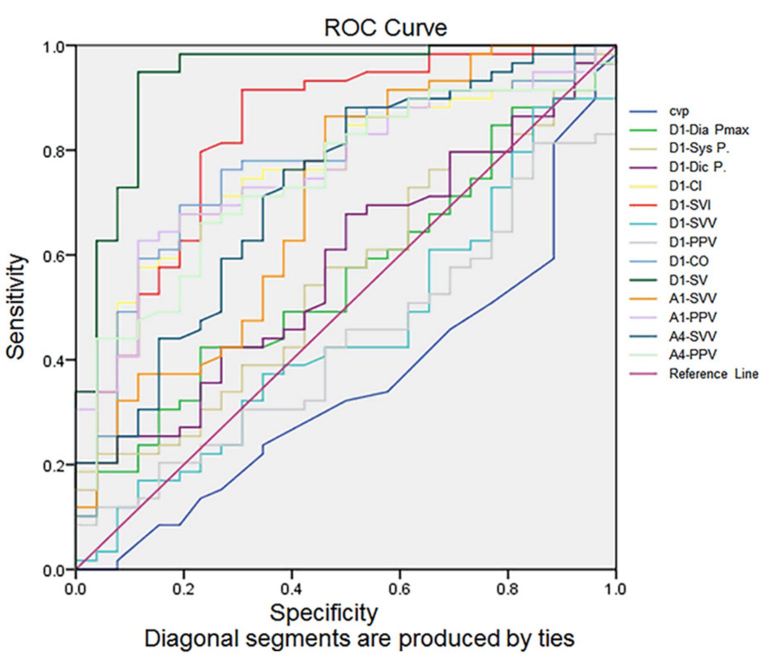

Figure 1. ROC curve of the percentage increases of SV, SVV, PPV, and other parameters.

vessels and state of microcirculation in abdominal organs and lower extremities would influence the volume that could be hired by PLR, while cardiac preload determined the actual effects of volume increase on hemodynamic changes. In venoconstriction caused by hypovolemia or cardiogenic shock, venous capacitance of the lower extremities and microcirculation were both reduced. Therefore, blood volume recruited by PLR was reduced, accordingly. In contrast, in peripheral vasodilatation caused by septic shock, blood volume recruited by PLR was increased. According to this theory, it could be concluded that PLR could induce less increases of right ventricular overload in patients with venoconstriction than those with septic shock. However, for patients highly-sensitive to fluid responsiveness, even moderate increases of preload could lead to significant increases of CO. This could be validated by the fact that, in healthy subjects, the influence of PLR on CO increases was more remarkable after their blood volume was reduced [4]. Affinities and Nouira have argued that the impact of the vasopressor on PLR could be ignored and PLR was still reliable in predicting fluid responsiveness, even in patients taking large amounts of vasopressors [26, 27]. Vasopressors only influence the amount of volume recruited. However, in this case, the patient had severely low preload. Thus, even a small amount of volume recruited could induce highly receptive fluid responsiveness.

The AUC value of SVV and PPV was not high and the diagnostic efficacy was significantly lower than that of PLR. Moreover, cut-off values for diagnosis in these two parameters (SVV: 9.2%; PPV: 11.2%) were consistent with previous studies [27].

Disclosure of conflict of interest

None.

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