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Original Contribution

Echocardiographic Characteristics Including Tissue Doppler Imaging After Enhanced External Counterpulsation Therapy

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This study assessed the effects of a course of enhanced external counterpulsation (EECP) therapy on systolic and diastolic cardiac function using echocardiography to measure left ventricular ejection fraction (LVEF), end-systolic volume (ESV), end-diastolic volume (EDV), systolic wave (Sm), early diastolic wave (Ea), Vp, E/Ea, E/Vp, and diastolic function grade in 25 patients before and after 35 hours of EECP. EECP reduced ESV and EDV and increased ejection fraction significantly in patients with baseline LVEF ≤50% (*P*=.018, .013, .002), baseline E/Ea ≥14 (*P*=.032, .038, .007), baseline grade II or III diastolic dysfunction (decreased compliance) (*P*=.014, .032, .027), baseline Ea <7 cm/s (*P*=.015, .024, .001), and baseline Sm <7 cm/s (*P*=.017, .016, .006), but not in patients with baseline LVEF >50%, baseline E/Ea <14, baseline normal diastolic function or grade I diastolic dysfunction (impaired relaxation), baseline Ea ≥7 cm/s, and Sm ≥7 cm/s. These results demonstrate improved systolic and diastolic function in selected patients and provide new insight into potential clinical applications of EECP. ©2007 Le Jacq

Enhanced external counterpulsation (EECP) has been studied for 45 years as a noninvasive method for the treatment of ischemic heart disease.[1,2] Recently, EECP has been used successfully as therapy for patients with chronic stable angina inadequately controlled with medication and unsuitable for percutaneous coronary intervention or coronary artery bypass graft surgery (CABG).[3–5] EECP increases time to exercise-induced ischemia, reduces angina frequency and nitroglycerin use, and improves Canadian Cardiovascular Society (CCS) classification and quality of life.[3,4,6–9] It has been reported that up to 15% of patients with angina meet the criteria for refractory angina.[10]

Although EECP is known to decrease symptoms in patients with angina, its role in patients with heart failure has only recently been investigated. Recent studies suggest that EECP increases exercise capacity by increasing peak oxygen uptake and exercise duration and improves functional status and quality of life in patients with heart failure. The US Food and Drug Administration cleared EECP therapy for the treatment of heart failure in 2002.[11–15]

EECP is associated with an immediate and long-lasting increase in the blood flow of coronary arterial circulation,[16,17] increasing endothelial shear stress[10] and enhancing endothelial function by stimulating the release of the vasodilatory mediator nitric oxide and reducing the release of vasocontractile endothelin-1.[18–20] Also, EECP stimulates collateral blood vessel development not only by increasing the release of angiogenesis factors such as vascular endothelial growth factor,[21] basic fibroblast growth factor, and hepatocyte growth factor,[18] but also by increasing monocyte chemoattractant protein 1 (a proinflammatory cytokine).

The present study sought to evaluate the effects of EECP on the echocardiographic parameters of systolic and diastolic function before and after a 35-hour course of EECP.

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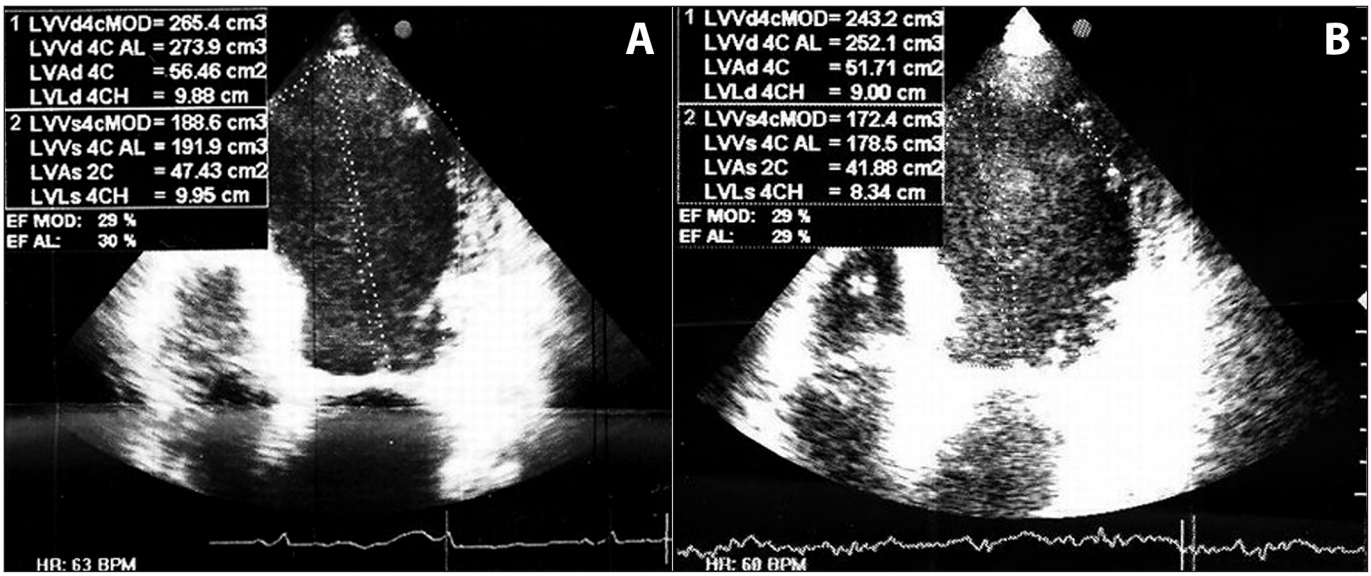

Figure 1. Left ventricular (LV) volume measurement before enhanced external counterpulsation (EECP) (A), and LV volume measurement after EECP (B).

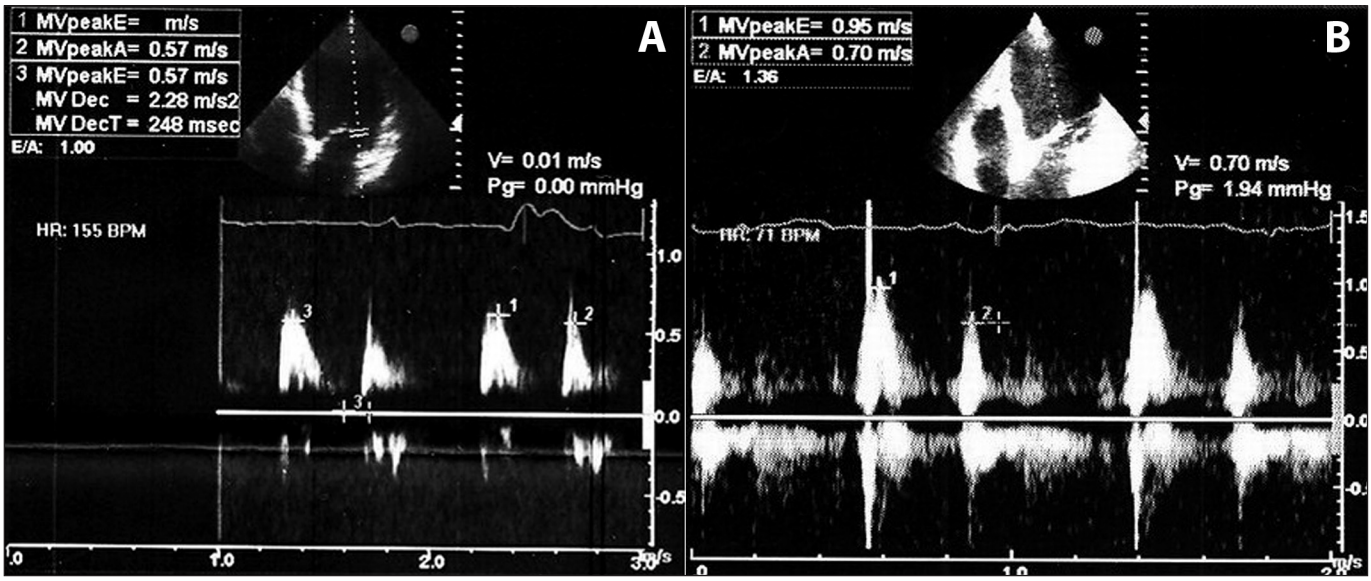

Figure 2. Pulsed Doppler assessment of left ventricular (LV) inflow before enhanced external counterpulsation (EECP) (A), and pulsed Doppler assessment of LV inflow after EECP (B).

Study Population

Twenty-five consecutive patients with refractory chronic, stable angina met the following inclusion criteria: (1) age older than 18 years; (2) symptoms of angina consistent with CCS classification I to III; (3) angiographically proven coronary artery disease; and (4) deemed a poor candidate for percutaneous coronary intervention or CABG.

Patients were excluded if they had any of the following: (1) unstable angina; (2) myocardial infarction in the preceding 6 weeks; (3) left ventricular ejection fraction (LVEF) <25%; (4) significant valvular disease; (5) overt heart failure; (6) left main lesion >50%; (7) blood pressure >180/100 mm Hg; (8) a permanent pacemaker or internal cardiac defibrillator; (9) atrial fibrillation rhythm or frequent premature ventricular contraction that interfered with EECP triggering; (10) severe peripheral vascular disease, phlebitis, or deep vein thrombosis; and (11) bleeding diathesis or warfarin use with an international normalized ratio >2.0.

Medication usage remained unchanged during this study, and patients underwent echocardiography before and after EECP therapy.

Methods

Enhanced External Counterpulsation. All patients were treated with an EECP therapy system (Vasomedical, Inc, Westbury, NY), comprised of

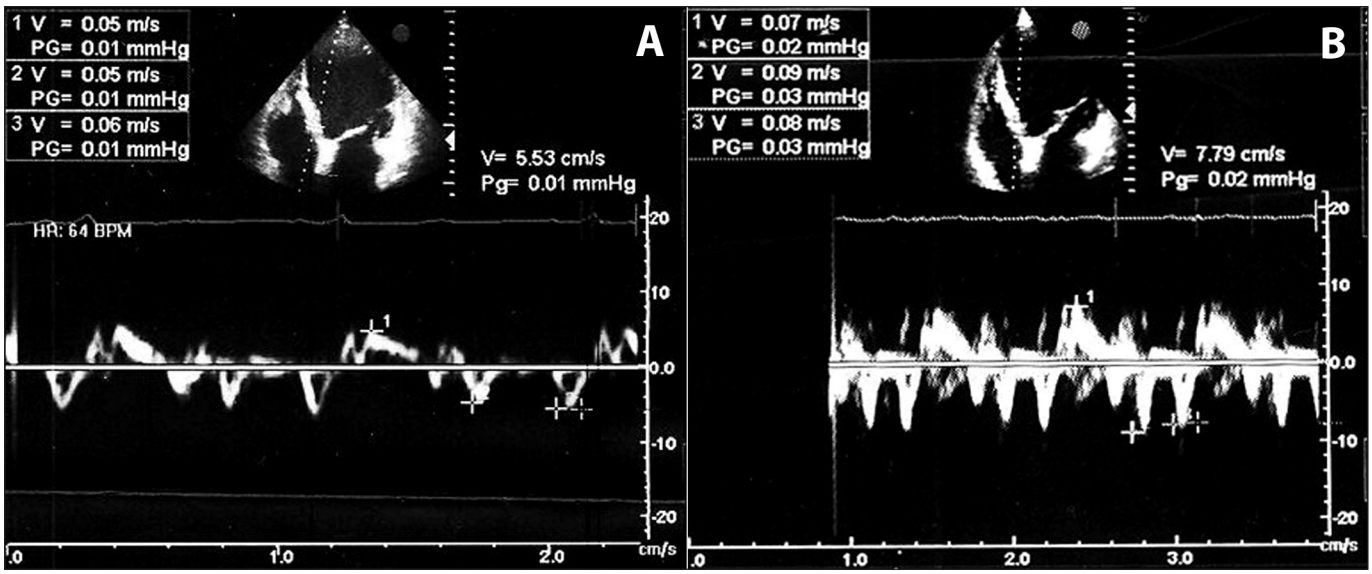

Figure 3. Tissue velocity of septal side of mitral annulus before enhanced external counterpulsation (EECP) (A), and tissue velocity of septal side of mitral annulus after EECP (B).

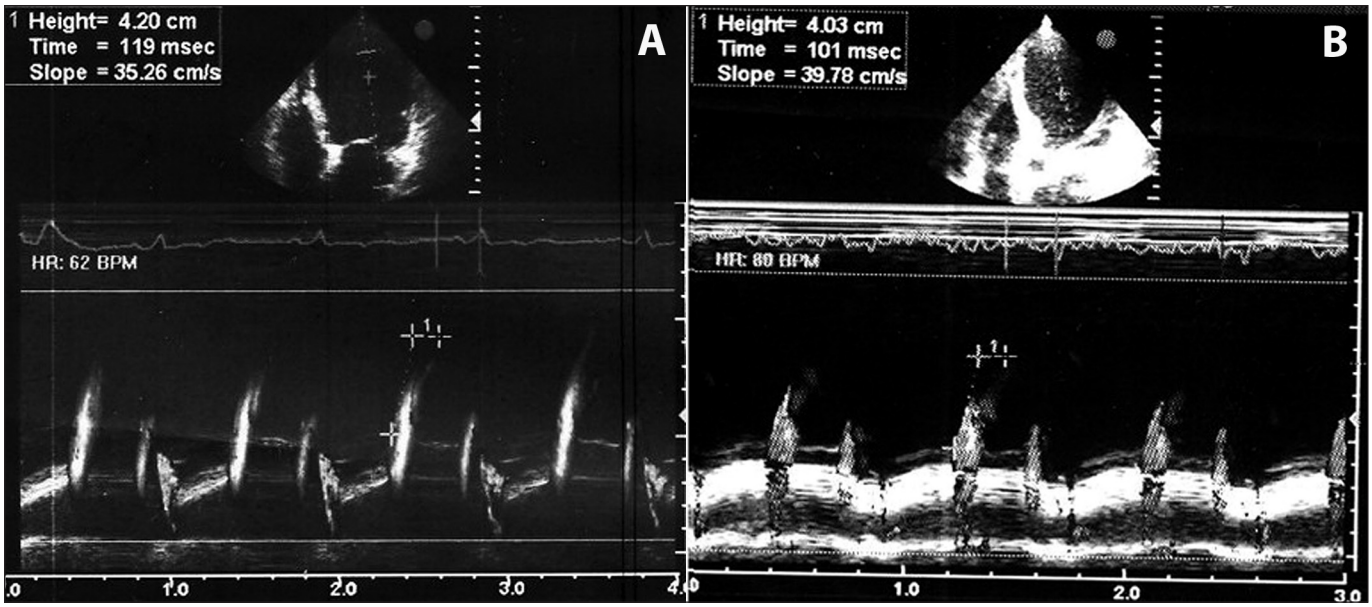

Figure 4. Mitral inflow propagation velocity before enhanced external counterpulsation (EECP) (A), and mitral inflow propagation velocity after EECP (B).

an air compressor, computer console, treatment table, and an integrated cuff set with 3 pairs of pneumatic cuffs. Before treatment, the cuffs were wrapped around the calves and lower and upper thighs of the patient, and echocardiographic leads were placed. In synchrony with the patient's cardiac cycle, the EECP system inflated the cuffs with air in a rapid sequence from the calves to the buttocks in early diastole, compressing blood vessels in the lower extremities and displacing venous and arterial blood toward the heart. At the end of diastole, the compressed air was released from all the cuffs simultaneously to rapidly remove the externally applied pressure and allow the vessels to reconform. Inflation increases diastolic blood pressure (diastolic augmentation) and venous return during diastole, while deflation reduces vascular impedance and cardiac workload during the subsequent systole. The EECP was applied every 35 hours divided into 60-minute sessions 5 days per week. During each session, the change in the patients' blood pressure wave was monitored by finger plethysmography. A cuff pressure of approximately 0.04 Pa was applied so that the ratio of plethysmographically measured

Table I. Baseline Characteristics

Mean age (range), y	57.8 (42–82)
Sex (male/female), No.	18/7
Coronary artery disease factors and revascularization status	
3-Vessel disease	18 (72)
2-Vessel disease	6 (24)
1-Vessel disease	1 (4)
Left ventricular ejection fraction	
>50%	12 (48)
31%–50%	8 (32)
<31%	5 (20)
Prior percutaneous coronary intervention	2 (8)
Prior coronary artery bypass graft surgery	16 (64)
Angina Canadian Cardiovascular Society classification	
I	5 (20)
II	13 (52)
III	7 (28)
IV	0

Values are expressed as No. (%) unless otherwise indicated.

diastolic peak pressure to systolic peak pressure was 1.5 times or higher.

Echocardiography. Standard echocardiographic examinations were carried out in accordance with the recommendations of the American Society of Echocardiography using a digital ultrasound machine (Vivid 3, GE Medical Systems, Inc, Milwaukee, WI) with the patient in the left, lateral decubitus position. A variable frequency-phased array transducer (2.5-3.5 to 4.0 MHz) was used for 2-dimensional, M-mode, and Doppler imaging. All measurements were analyzed using the average of ≥3 cardiac cycles. Two-dimensional measurements of left ventricular (LV) volume were obtained from the apical 4-chamber view at end-diastole and end-systole, and LVEF was calculated using the modified Simpson method (Figure 1).

Pulsed Doppler assessment of LV inflow was performed in the apical 4-chamber view with the sample volume placed at the level of the valve tips. The following measurements of global LV diastolic function were determined: peak velocity of the E and A waves and the E/A ratio, deceleration time of the E wave (in ms), and isovolumic relaxation time (in ms) measured as the time interval occurring between the end of systolic output flow and transmittal E-wave onset by placing pulsed Doppler sample volume between the outflow tract and the mitral valve (Figure 2).

Pulsed Doppler Myocardial Imaging. Pulsed Doppler myocardial imaging was performed by spectral pulsed Doppler signal filters by adjusting the Nyquist limit within 15 to 20 cm/s (close to myocardial velocities) and using minimal optimal gain. In the apical 4-chamber view, a 3.5-mm pulsed Doppler sample volume was placed on the basal septum of the LV at the level of mitral annulus. Myocardial systolic wave (Sm) and early diastolic wave (Ea) were measured (Figure 3).

Diastolic Function Grading. Normal LV diastolic function was diagnosed if the peak early diastolic transmitral flow velocity (E)/peak late diastolic transmitral flow velocity (A) ratio was between 0.75 and 1.5 and the E/Ea ratio was <10. Mild LV diastolic dysfunction was diagnosed if the E/A ratio was <0.75 regardless of the E/Ea ratio. Moderate LV diastolic dysfunction was diagnosed if the E/A ratio was between 0.75 and 1.50 and the mitral E/peak early diastolic myocardial velocity (Ea) ratio was >10. Severe LV diastolic dysfunction was diagnosed if the E/A ratio was >1.5 and the E/Ea ratio was >10.

Color Doppler M-Mode Imaging. Mitral inflow propagation velocity was evaluated from the apical 4-chamber view using color flow imaging to place a color M-mode cursor parallel to mitral inflow in the center of the flow stream. The aliasing velocity of 0.5 to 0.7 m/s and signal was recorded at a fast sweep speed (100–200 mm/s). The slope of the first aliasing velocity from the mitral valve to LV was measured (Figure 4).

Statistical Analyses. All values were expressed as mean ± SD. The paired *t* test method was used to compare pretreatment with posttreatment values, and statistical significance was determined at a level of $P<.05$.

Results

Twenty-five consecutive patients presenting for EECP therapy were enrolled in this study. Mean age of the patients was 57.8±9 years (range, 42–82 years) and 18 were men (72%). Eighteen patients (72%) had 3-vessel disease, 6 patients (24%) had 2-vessel disease, and 1 patient (4%) had single-vessel disease. Sixteen patients had a history of CABG (64%) (Table I).

Mean baseline end-diastolic volume (EDV) was 125.08±67.5 mL and end-systolic volume (ESV) was 73.6±60 mL, both of which reduced significantly after EECP therapy to 105±58.4 mL and 59.8±47.2 mL, respectively (both $P<.01$). Mean LVEF was 46%±12.6% at baseline, which increased significantly to 51.5%±12% ($P<.01$). Mean baseline Ea and Sm were 10±5.7 cm/s and 9±5.44 cm/s, respectively, and showed no significant change after

Table II. Changes in Left Ventricular Function After EECP

	Pre-EECP	Post-EECP	*P* Value
LVEF, %	46±12.6	51.5±12	<.01
LVEDV, mL	125.08±67.5	105±58.4	<.01
LVESV, mL	73.6±60	59.8±47.2	<.01

Abbreviations: EECP, enhanced external counterpulsation; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-diastolic volume.

EECP. Mean propagation velocity, E/Ea, and E/Vp before treatment were 42.40±13.79, 15.6±7.46, and 2.05±0.90, respectively, and showed no change after EECP therapy. Mean diastolic function grade was 2.24±1.26 pretreatment and exhibited no significant change after therapy (Table II).

In a secondary set of analyses, patients were divided according to whether their baseline values fell above or below prespecified thresholds. EECP reduced ESV and EDV and increased LVEF significantly (P=.018, .013, .002, respectively) in patients with a baseline LVEF ≤50%, while there was no such change in patients with a baseline LVEF >50%.

Patients with E/Ea <14, who were expected to have low left atrial pressure, had no improvement in EDV, ESV, and LVEF after EECP treatment, whereas patients with E/Ea ≥14, who were expected to have elevated left atrial pressure had a significant reduction in EDV and ESV (P=.038 and P=.032, respectively) and an increase in LVEF (P=.007). Similarly, patients with normal diastolic function or mild diastolic dysfunction (impaired relaxation) had no significant change in EDV, ESV, and LVEF after EECP treatment, while patients with moderate to severe diastolic dysfunction (decreased LV compliance) had significantly improved ESV, EDV, and LVEF (P=.014, .032, .027, respectively).

Patients with Ea <7 cm/s before EECP showed a significant improvement in EDV, ESV, and LVEF after therapy (P=.024, .015, .001, respectively), while patients with Ea ≥7 cm/s exhibited no significant change. Similarly, patients with baseline Sm <7 cm/s showed a significant improvement in EDV, ESV, and LVEF after EECP (P=.016, .017, .006, respectively), while patients with Sm ≥7 cm/s showed no significant change after EECP.

Discussion

The present study is one of the first echocardiographic studies of patients treated with EECP for chronic stable refractory angina pectoris focusing on tissue Doppler imaging. Findings in this study demonstrated that EECP significantly increases LVEF and decreases EDV and ESV (Figure 1). Therefore, systolic function and LV volumes improve after EECP therapy.

Urano and colleagues[22] reported that EECP treatment improved not only LV dilation, but also myocardial blood flow. EECP treatment is also associated with an immediate increase in blood flow in multiple vascular beds, including the coronary arterial circulation.[16] As a result, EECP increases endothelial shear stress by increasing blood flow,[10] which enhances endothelial function[7] by stimulating the release of vasodilatory mediator nitric oxide and reducing the release of vasocontractile endothelin-1.[18–20] These changes are progressive during the course of therapy[23] and serve to explain improved coronary perfusion and vasodilation after EECP.

The result of this study shows no significant change in diastolic function parameters such as Ea, propagation velocity, E/Ea, E/Vp, and diastolic function grade (Figure 2, Figure 3, and Figure 4). Similarly, in a recent study, no significant change in fractional shortening and diastolic function was observed. There was a reduction in the area of inducible ischemia at dobutamine stress echocardiography after EECP; nevertheless, due to a small sample size, the area was not significantly different.[24]

It was noted that the patients with lower LVEF (≤50%) and Sm velocity of the septal annulus (<7 cm/s) had more significant change in LVEF, EDV, and ESV than the patients with higher E/Ea (≥14) and lower Ea velocity of septal annulus (<7 cm/s). Therefore, the patients in our study with more advanced systolic and diastolic dysfunction and higher LV end-diastolic pressure and left atrial pressure had more improvement in LVEF, EDV, and ESV, which is in accordance with results reported by Novo and colleagues[24] regarding a trend that patients who benefited most were those with worse systolic function and severely compromised segmental kinesis.

Results from this study provide new insight into the hemodynamic effects of EECP therapy in patients with coronary artery disease and either preserved or impaired left ventricular function. Effects of this safe, noninvasive therapy in individual patients can be more readily anticipated, and clinical application of EECP may be able to be more specifically prescribed.

Disclosure: Dr Soran serves on the scientific Speakers' Bureau of Vasomedical Inc.

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