Enhanced external counterpulsation increases coronary flow reserve in coronary microvascular disease

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ABSTRACT

الأهداف: تبحث هذه الدراسة في آثار النبض الخارجي المعزز (EECP) في المرضى الذين يعانون من مرض الأوعية الدموية الدقيقة التاجية (CMD).

المنهجية: قسمنا المرضى الذين يعانون من CMD إلى مجموعة EECP (العدد = 41) ومجموعة مراقبة (العدد = 42). أجرينا قياس احتياطي التدفق التاجي (CFR) قبل وبعد برنامج EECP لمدة أربعة أسابيع باستخدام تخطيط صدى القلب دوبلر عبر الصدر. كما أجرينا تحليل مستويات مصل سينسيز أكسيد النيتريك البطاني (eNOS) و endothelin–1 (ET–1) بواسطة ELISA. قيمنا جودة الحياة من خلال استبيان سياتل للذبحة الصدرية (SAQ) وفئة الذبحة الصدرية التابعة لجمعية القلب والأوعية الدموية الكندية (CCS).

النتائج: ارتفع معدل CFR بشكل ملحوظ في مجموعة EECP بعد أربعة أسابيع مقارنة مع مجموعة المراقبة ($p<0.05$). انخفض endothelin–1 بشكل كبير وارتفع eNOS بشكل ملحوظ في مجموعة EECP. كما عززت EECP نتائج SAQ للمرضى وانخفضت فئة الذبحة الصدرية CCS.

الخلاصة: قام EECP بتحسين احتياطي التدفق التاجي وتحسين جودة الحياة لدى المرضى الذين يعانون من CMD.

Objectives: To investigates the outcomes of enhanced external counterpulsation (EECP) among coronary microvascular disease (CMD) patients.

Methods: Coronary microvascular disease patients were separated into the EECP (n=41) and control cohorts (n=42). Prior to and following the 4-week EECP program, coronary flow reserve (CFR) was recorded using transthoracic Doppler echocardiography. The serum endothelial nitric oxide synthase (eNOS) and endothelin-1 (ET-1) contents were analyzed by ELISA. Quality of life (QoL) was assessed by the Seattle Angina Questionnaire (SAQ) and the Canadian Cardiovascular Society (CCS) angina class.

Results: After four weeks, CFR was substantially enhanced in the EECP versus control cohort ($p<0.05$). Endothelin-1 was strongly diminished whereas eNOS was considerably upregulated in the EECP cohort. EECP also enhanced patients' SAQ scores and decreased the CCS angina class.

Conclusion: Enhanced external counterpulsation may improve CFR and enhance the CMD patient QoL.

Keywords: enhanced external counterpulsation, coronary flow reserve, coronary microvascular disease, endothelial function

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Angina is a frequently occurring clinical manifestation among obstructive coronary artery disease (CAD) patients, and it contributes to a majority of global disease-related mortality rate. However, more than 50% angina patients have no obstructive CAD, and a large proportion of angina patients have coronary microvascular dysfunction; this kind of disease which damages coronary microcirculation is termed coronary microvascular disease (CMD).[1-5] According to the Coronary Vasomotion Disorders International Study Group's definition, a CMD diagnosis involves symptomology and presence of myocardial ischemia, as well as lack of obstructive CAD, along with significant CMD.[6]

Coronary microvascular disease is correlated with undesired cardiovascular complications.[7] However, there are currently no effective therapies targeting CMD and no guidelines on the management of CMD.[8] Enhanced external counterpulsation (EECP) is an effective non-medication intervention for CAD and can reduce angina, increase myocardial perfusion, and ameliorate endothelial dysfunction in CAD patients.[9,10] Increased vascular resistance and endothelial dysfunction are two important pathogenic factors in CMD.[11] External counterpulsation may ameliorate angina by improving myocardial perfusion and endothelial function in CMD patients, but whether EECP is beneficial for patients with CMD has not been explored.

As an indicator of coronary microvascular activity, coronary flow reserve (CFR) could be determined using an invasive technique, such as Doppler wire or non-invasive method. Coronary flow reserve measured by transthoracic echocardiography (TTE) is a non-invasive method. It is harmfuless and has reliable result. In this study, we used CFR by transthoracic echocardiography Doppler to evaluate microvascular function. Here, we investigate the effects of EECP in patients with CMD and explore whether EECP may improve CFR in these patients.

Methods. This investigation was designed as a prospective randomized control trial. Eighty-three patients whose main complaint was angina pectoris were enrolled between March 2019 and December 2022, in Qinhuangdao First Hospital, Hebei, China. All patients underwent coronary angiography and presented with normal epicardial coronary arteries. After this initial selection, the diagnosis of CMD was confirmed by assessment of CFR. The main inclusion criteria included were i) aged 30-75 years; ii) symptoms of chest pain or dyspnea; iii) objective documentation of myocardial ischemia, such as electrocardiogram, exercise experiments, or echocardiography; iv) CFR <2.0; v) coronary artery stenosis of less than 50% assessed by coronary angiography. Exclusion criteria included i) patients with obstructive CAD; ii) prior myocardial infarction; iii) patients with carcinoma; iv) patients with atrial fibrillation; v) patients with hypertrophic cardiomyopathy; vi) dilated cardiomyopathy patients; vii) contraindications of EECP, such as unregulated hypertension (SBP ≥180 mmHg or DBP ≥100 mmHg), aortic dissection, or lower extremity deep vein thrombosis. This study received ethical approval from the Qinhuangdao First Hospital, and obtained signed informed consent from all participants.

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Assessment of CFR. Coronary flow reserve was evaluated via transthoracic Doppler echocardiography (VIVID 9 Ultrasound System, GE) in all patients at baseline and 4 weeks after EECP treatment. Echocardiography was carried out by a skilled echocardiographer, who had no knowledge of the patient clinical information. Caffeine and nitroglycerin were forbidden for 24 hours before the examination. Left ventricular diameter (LVD) and left atrial diameter (LAD) were recorded, and the left ventricular ejection fraction (LVEF) was computed via the biplane Simpson technique.

Coronary flow in the left anterior descending artery (LAD) was determined using color Doppler and an apical 5-chamber view (distal of LAD) or by a modified low short-axis view (mid-distal of LAD).[12] Baseline coronary flow velocity was measured. Adenosine was infused via the median cubital vein (140 μg/kg/minute [min] for 2 min), and the hyperemic peak diastolic velocity was measured. The CRF was computed as the hyperemic peak diastolic velocity (PDV) to baseline PDV ratio.

Enhanced external counterpulsation treatment. Eighty-three CMD patients were arbitrarily separated into the EECP (n=41) and control cohorts (n=42). Enhanced external counterpulsation patients received EECP treatment 6 days per week for 4 consecutive weeks using a cuff inflation pressure of 250 mmHg. The EECP was performed via an oxygen saturation monitoring EECP Instrument (Chongqing PSK Health, China). Patients of both groups received medication (100 mg aspirin daily, 20 mg atorvastatin daily, and 5 mg nicorandil 3 times per day).

Laboratory measurements. Baseline and four week venous blood samples were acquired from all participants. Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and glucose were recorded. Serum endothelial nitric oxide synthase (eNOS) and endothelin-1 (ET-1) concentrations were assessed via ELISA kits (Zhuocai Biotech, Shanghai, China) as per kit directions.

Quality of life (QoL) evaluation. Baseline and four week post EECP treatment QoL were evaluated using the Seattle Angina Questionnaire (SAQ). The Canadian Cardiovascular Society (CCS) angina class was evaluated at the same time points as well.

Statistical analysis. Data analyses employed the SPSS, version 20 (IBMCorp, Armonk, NY, USA). Continuous data, evaluated via the Student's t test, are provided as the mean ± standard deviation. Comparisons between baseline and four weeks post intervention were performed via the paired t test. Categorical information was assessed using the $\chi 2$ statistics or Fisher's exact test. $p \leq 0.05$ was considered significant.

Results. ***Clinicopathological profiles of groups.*** Eighty-three patients meeting our strict inclusion and exclusion guidelines were recruited for analysis. As shown in Table 1, no marked differences were present in the baseline or four week post treatment clinical characteristics between the EECP and control cohorts (all $p>0.05$).

Enhanced external counterpulsation treatment improves the CFR. As depicted in Figure 1, no discernible difference appeared in baseline CFR between the EECP and control cohorts (EECP 1.74 ± 0.23, control 1.67 ± 0.31, $p>0.05$). After the four-week program, patients in the EECP group had higher CFR values than the control group (EECP 2.34 ± 0.37, control 1.85 ± 0.37, $p<0.05$).

EECP treatment increases eNOS and decreases ET-1. As depicted in Figure 2, after 4 weeks, the eNOS contents were increased in the EECP versus baseline and control cohorts ($p<0.05$). No difference was present in the eNOS level between the baseline and after 4 weeks among controls. After 4 weeks, the ET-1 levels were diminished among the EECP versus baseline ($p<0.05$) and control cohorts ($p<0.05$).

Enhanced external counterpulsation relieves angina and enhances patients' QoL. As shown in Figure 3, the CCS angina class decreased in both groups after 4 weeks compared with their baselines ($p<0.05$). However, EECP patients experienced reduced CCS angina class values relative to the control patients ($p<0.05$). After 4 weeks, the EECP patients demonstrated increased SAQ scores relative to the control participants ($p<0.05$; Table 2).

Discussion. Herein, we demonstrated that 4 weeks of EECP treatment greatly enhances CFR and relieve angina in patients with CMD.

Enhanced external counterpulsation is a noninvasive intervention to ameliorate the symptoms of angina pectoris and to relieve hypoxia-ischemia. It is frequently employed for CAD and heart failure treatment. Many studies demonstrate that external counterpulsation relieves angina and improves maximal walking capacity and cardiac function.[13,14] Jan et al[15] explored the effect of EECP on patients with severe CHD who were unsuitable for revascularization and found that EECP therapy could improve patients' QoL. Du et al[16] found that EECP combined with exercise therapy induced collateral circulation formation. However there is no study to explore the therapy effect of EECP in CMD patients.

Herein, our results demonstrated that EECP relieved angina and improved patients' QoL. After 4 weeks of EECP treatment, the CCS angina class was decreased

Table 1 - Evaluation of the clinicopathological profiles of control and EECP treated cohorts.

Parameters	EECP group (n=41)	Control group (n=42)	*P*-value
Age (years)	60.85 ± 8.44	59.52 ± 8.67	0.481
Gender (male/ female)	20/21	17/25	0.447
Hypertension	25/41	25/42	0.893
Diabetes	10/41	7/42	0.383
Smoker	10/41	11/41	0.850
SBP (mmHg)			
baseline	135.90 ± 17.87	133.26 ± 16.43	0.485
4 weeks	137.76 ± 11.45	135.33 ± 12.81	0.415
DBP (mmHg)			
baseline	78.98± 12.25	82.76 ± 11.94	0.158
4 weeks	79.86 ± 12.97	80.04 ± 10.99	0.434
TC (mmol/L)			
baseline	4.28 ± 0.96	4.32± 1.12	0.380
4 weeks	4.31 ± 0.72	4.27 ± 0.79	0.361
TG (mmol/L)			
baseline	1.83 ± 1.08	2.07 ± 1.22	0.167
4 weeks	1.76 ± 0.66	1.93 ± 0.76	0.214
LDL-C (mmol/L)			
baseline	2.32 ± 0.75	2.36 ± 0.78	0.179
4 weeks	2.33 ± 0.81	2.31 ± 0.93	0.256
HDL-C (mmol/L)			
baseline	1.10 ± 0.30	0.96± 0.22	0.135
4 weeks	1.12 ± 0.26	1.04 ± 0.31	0.178
FBS (mmol/L)			
baseline	5.52 ± 0.79	5.88 ± 1.23	0.136
4 weeks	5.45 ± 1.67	5.67± 1.33	0.247
Body mass index			
baseline	25.82 ± 2.86	26.59 ± 2.68	0.213
4 weeks	25.67 ± 2.71	26.54 ± 2.30	0.315
LVD (mm)			
baseline	48.05 ± 3.59	48.51 ± 5.34	0.646
4 weeks	47.89 ± 4.30	48.65 ± 5.67	0.357
LAD (mm)			
baseline	36.49 ± 3.76	37.90 ± 5.24	0.165
4 weeks	37.01 ± 3.78	37.44 ± 5.61	0.412
LVEF (%)			
baseline	67.81 ±5.15	65.26 ± 6.87	0.127
4 weeks	66.35 ± 7.24	66.02± 7.30	0.348

EECP: enhanced external counterpulsation, SBP: systolic blood pressure, DBP: diastolic blood pressure, TC: cholesterol, TG: triglyceride, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, FBS: fasting blood glucose

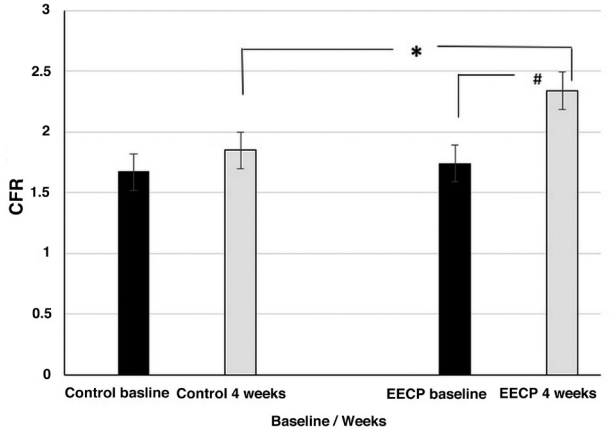

Figure 1 - Coronary flow reserve (CFR) improvement after 4 weeks of enhanced external counterpulsation (EECP). **P*<0.05 relative to control, #*p*<0.05 relative to baseline

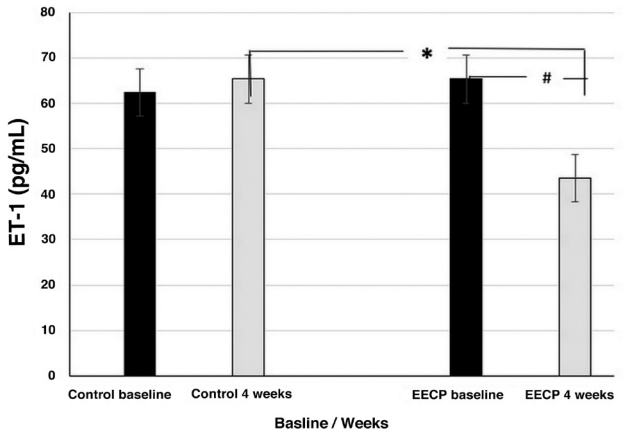

Figure 3 - Changes of endothelin-1 (ET-1) after 4 weeks enhanced external counterpulsation (EECP). **P*<0.05 relative to control, #*p*<0.05 relative to baseline

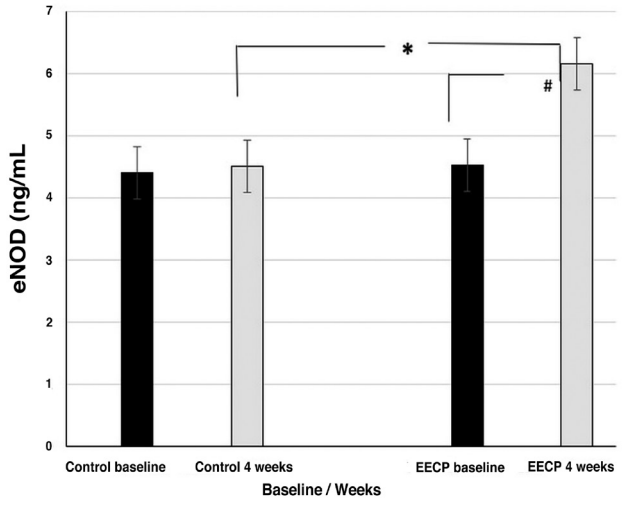

Figure 2 - Changes of endothelial nitric oxide synthase (eNOS) after 4 weeks enhanced external counterpulsation (EECP). **P*<0.05 relative to control, #*p*<0.05 relative to baseline

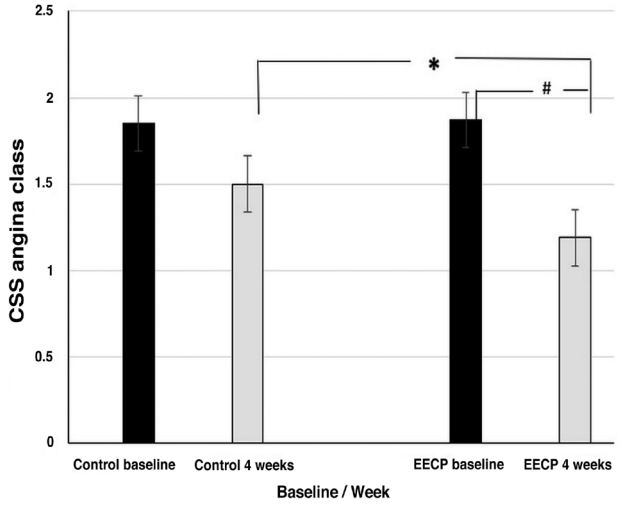

Figure 4 - Changes of Canadian Cardiovascular Society (CCS) angina class after 4 weeks enhanced external counterpulsation (EECP). **P*<0.05 relative to control, #*p*<0.05 relative to baseline

among EECP versus baseline and control cohorts, while the SAQ score increased in the EECP group.

Microcirculation dysfunction limits myocardial perfusion in patients with CMD, and because CFR reflects the vasodilatory ability of the coronary microcirculation, it is a valuable indicator of CMD.[17] In the absence of obstructive CAD, a CFR <2.0 is abnormal and is a critical basis of CMD diagnosis.[6] This study demonstrates that four weeks of EECP treatment increased the CFR value, which indicates that EECP may relieve coronary microcirculation dysfunction.

The serum level of eNOS increased after 4 weeks in the EECP group while the ET-1 level decreased. Nitric oxide promotes vasorelaxation and maintains endothelial function, and decreased nitric oxide is associated with microcirculation dysfunction.[18] Our results indicate that the benefits of EECP for patients with CMD may be attributable to an improvement in coronary flow and microvascular endothelial function.

The mechanisms of CMD are not fully understood, but limited myocardial perfusion, endothelial dysfunction, Systemic infammation and microvascular remodeling may serve an essential function in it. The conventional CMD treatments include anti-angina and anti-atherosclerosis therapy, such as aspirin, statins

Table 2 - Quality of life (QoL) evaluated by Seattle Angina Questionnaire score.

	EECP group (n=41)	Control group (n=42)	P-value
Physical limitation			
baseline	34.34 ± 6.84	33.71 ± 6.71	0.674
4 weeks	42.65 ± 7.24*†	35.59 ± 7.61	0.000
Angina stability			
baseline	32.85 ± 6.61	33.61 ± 6.08	0.585
4 weeks	43.90 ± 6.34*†	36.35 ± 5.77†	0.000
Angina frequency			
baseline	37.17 ± 5.67	37.59 ± 5.99	0.741
4 weeks	47.53 ± 6.51*†	42.01 ± 5.29†	0.000
Treatment satisfaction			
baseline	43.95 ± 6.57	44.19 ± 7.05	0.873
4 weeks	55.43 ± 6.81*†	48.78 ± 8.38†	0.000
Disease perception			
baseline	29.73 ± 4.84	28.47 ± 6.42	0.319
4 weeks	43.39 ± 5.94*†	32.76 ± 6.73†	0.000

*P<0.05 compared with control, †P<0.05 compared with baseline. EECP: enhanced external counterpulsation

and Nicorandil. As we know, EECP could increase myocardial perfusion and ameliorate endothelial dysfunction. These maybe possible mechanisms that EECP could have effectiveness in patients with CMD.

Study limitations. First, this is a single-center trial that explored EECP treatment of patients with CMD. However, the trial was unable to determine differences in the clinical outcomes between the EECP and control cohorts because of the small number of patients. Second, flow-mediated dilation was not used to assess endothelial function in patients with CMD. Third, external counterpulsation-related mechanisms are complex and we did not explore these mechanisms. Additional investigations are required to confirm the benefits of EECP intervention in patients with CMD.

In conclusion, this study demonstrates that EECP treatment maybe improve CMD patients' CFR. Additionally, we demonstrated marked enhancements in treated patients' CCS angina class and QoL. Our results provide strong basis for additional investigations into EECP therapy as a possible strategy in CMD and non-obstructive CAD patients.

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References

1. Ford TJ, Stanley B, Good R, Rocchiccioli P, McEntegart M, Watkins S, et al. Stratified medical therapy using invasive coronary function testing in angina: The CorMicA trial. *J Am Coll Cardiol* 2018; 72: 2841-2855.
2. Sara JD, Widmer RJ, Matsuzawa Y, Lennon RJ, Lerman LO, Lerman A. Prevalence of coronary microvascular dysfunction among patients with chest pain and nonobstructive coronary artery disease. *JACC Cardiovasc Interv* 2015; 8 :1445-1453.
3. Taqueti VR, Solomon SD, Shah AM, Desai AS, Groarke JD, Osborne MT, et al. Coronary microvascular dysfunction and future risk of heart failure with preserved ejection fraction. *Eur Heart J* 2018;39: 840-849.
4. Jürs A, Pedersen LR, Olsen RH, Snoer M, Chabanova E, Haugaard SB, et al. Coronary microvascular function, insulin sensitivity and body composition in predicting exercise capacity in overweight patients with coronary artery disease. *BMC Cardiovasc Disord* 2015; 15: 159.
5. Taqueti VR, Di Carli MF. Coronary microvascular disease pathogenic mechanisms and therapeutic options: JACC state-of-the-art review. *J Am Coll Cardiol* 2018; 72: 2625-2641.
6. Bradley C, Berry C. Definition and epidemiology of coronary microvascular disease. J Nucl Cardiol. 2022;29(4):1763-1775.
7. Chen C, Wei J, AlBadri A, Zarrini P, Bairey Merz CN. Coronary microvascular dysfunction—epidemiology, pathogenesis, prognosis, diagnosis, risk factor, and therapy. *Circ J* 2016; 81: 3–11.
8. Sinha A, Rahman H, Pereracorresponding D. Coronary microvascular disease: current concepts of pathophysiology, diagnosis and management. *Cardiovasc Endocrinol Metab* 2020; 10: 22-30.
9. Qin X, Deng Y, Wu D, Yu L, Huang R. Does enhanced external counterpulsation (EECP) significantly affect myocardial perfusion? A systematic review & meta-analysis. *PLoS One* 2016; 11: e0151822.
10. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, et al. 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: executive summary: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation* 2022; 145: e4-e17.

11. Ford TJ, Ong P, Sechtem U, Beltrame J, Camici PG, Crea F, et al. Assessment of vascular dysfunction in patients without obstructive coronary artery disease: Why, how, and when. ***JACC Cardiovasc Interv*** 2020; 13: 1847-1864
12. Tagliamonte E, Cirillo T, Rigo F, Astarita C, Coppola A, Romano C, et al. Ivabradine and bisoprolol on doppler-derived coronary flow velocity reserve in patients with stable coronary artery disease: Beyond the heart rate. ***Adv Ther*** 2015; 32: 757-767.
13. Yang H, Song L, Ning X, Ma Y, Xue A, Zhao H, Du Y, Lu Q, Liu Z, Wang J. Enhanced external counterpulsation ameliorates endothelial dysfunction and elevates exercise tolerance in patients with coronary artery disease. ***Front Cardiovasc Med*** 2022; 9: 997109.
14. Zhang Y, Chen Z, Mai Z, Zhou W, Wang H, Zhang X, et al. Acute hemodynamic responses to enhanced external counterpulsation in patients with coronary artery disease. ***Front Cardiovasc Med*** 2021; 8: 721140.
15. Jan R, Khan A, Zahid S, Sami A, Owais SM, Khan F, Asjad SJ, Jan MH, Awan ZA. The Effect of Enhanced External Counterpulsation (EECP) on quality of life in patient with coronary artery disease not amenable to PCI or CABG. ***Cureus*** 2020; 12: e7987.
16. Du F, Zhang W, Mao H, Guo Y, Guo M, Lu Y, Chen M, Sha Z. The Effect of long-term external counterpulsation combined with exercise therapy on the establishment of collateral circulation in patients with coronary artery occlusive disease. ***Biomed Res Int*** 2022; 2022: 1336184.
17. Ong P, Camici PG, Beltrame JF, Crea F, Shimokawa H, Sechtem U, et al. International standardization of diagnostic criteria for microvascular angina. ***Int J Cardiol*** 2018; 250: 16-20.
18. Thakker RA, Rodriguez Lozano J, Rodriguez Lozano P, Motiwala A, Rangasetty U, Khalife W, et al. Coronary microvascular disease. ***Cardiol Ther*** 2022; 11: 23-31.