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Enhanced External Counterpulsation Reduces Lung/Heart Ratio at Stress in Patients with Coronary Artery Disease

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Key Words
Enhanced external counterpulsation · Thallium-201 single-photon emission computed tomography · Lung/heart ratio

Abstract
Enhanced external counterpulsation (EECP) is a recently approved treatment modality for patients with angina and heart failure. However, the efficacy of EECP on left ventricular (LV) function has not been well established. The study was aimed to determine whether EECP leads to an improvement in objective parameters of LV function. Patients with coronary artery disease (n = 10) who showed evidence of stress-induced myocardial ischemia despite conventional medical or surgical therapies were enrolled and received EECP therapy for a total of 35 h. The therapeutic effects of EECP were examined by thallium-201 single-photon emission computed tomography (^{201}Tl-SPECT). Compared with baseline, the lung/heart ratio at stress decreased significantly from 0.40 ± 0.08 to 0.35 ± 0.08 (p = 0.001) at 1 month and 0.33 ± 0.10 (p = 0.03) at 6 months following EECP treatment. LV ejection fraction marginally improved from 56.7 ± 7.7% to 57.6 ± 5.9% (p = 0.382) at 1 month and to 60.1 ± 8.6% (p = 0.062) at 6 months after EECP therapy, although not statistically significant. We concluded that EECP improved LV function, shown as the reduction of lung/heart ratio at stress, in patients with coronary artery disease, up to 6 months after EECP treatment.

Introduction

New therapeutic treatments are emerging for the increasing number of patients with chronic angina and congestive heart failure that have been refractory to conventional pharmacological and interventional approaches. Enhanced external counterpulsation (EECP) is a recently approved treatment modality for patients with angina and heart failure [1–8]. In patients with chronic stable angina, objective evidences for the efficacy of EECP include improvement in time to ST-segment depression [2] in stress-induced myocardial ischemia using radionuclide perfusion treadmill tests [3, 4].

EECP is also a safe treatment in patients with coronary artery disease (CAD) and severe left ventricular (LV) dysfunction. EECP effectively improves angina symptoms and quality of life. These benefits are maintained at 6 months after EECP treatment [6]. The efficacy results in a recent study for patients with symptomatic heart failure

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suggested that EECP can improve exercise capacity, quality of life and functional status both in short term and also for 6 months after completion of the EECP therapy [7].

Recently, a multicenter, prospective, randomized, controlled clinical trial to verify the efficacy of EECP as an adjunctive therapy in the management of patients with chronic stable heart failure has been finalized [8]. The preliminary data indicates that EECP improves exercise tolerance (Feldman et al., ACC Scientific Meeting 2005).

Stress thallium-201 single-photon emission computed tomography (^{201}Tl-SPECT) is a well-established method for the detection of CAD. In addition to the reversible and fixed perfusion defects of myocardium, the incremental value of lung/heart ratio (LHR) has been reported to reflect LV decompensation, which could be due to an increase in end-diastolic volume and pressure [9, 10]. Even in patients with normal LV systolic function and myocardial perfusion, elevated ^{201}Tl lung uptake, especially in response to stress, is a marker of elevated filling pressure which probably reflects LV diastolic dysfunction [11].

To establish an objective marker for evaluating the therapeutic effects of EECP on LV dysfunction, we did a prospective study of CAD patients treated with EECP and analyzed their response to therapy by ^{201}Tl-SPECT prior to and at 1 and 6 months after completion of EECP treatment.

Methods

Design and Eligibility

A total of ten patients with documented CAD despite conventional medical or surgical therapies were consecutively enrolled in this study. Evidence of CAD required at least one of the following: (1) significant stenosis (>70% of luminal diameter) in at least one major coronary artery proved by angiography and had undertaken either percutaneous coronary intervention or coronary artery bypass graft (CABG); (2) positive stress myocardial perfusion imaging studies for ischemia. Patients were not included if any of the following were present: myocardial infarction or CABG in the preceding 3 months, unstable angina, significant valvular heart disease, blood pressure >180/100 mm Hg, unprotected left main stenosis greater than 50%, severe symptomatic peripheral vascular disease, deep vein thrombosis, atrial fibrillation or frequent ventricular premature beats that would interfere with EECP triggering. All patients provided written informed consent before the procedure. The protocol and consent were approved by the Institutional Review Boards at National Taiwan University Hospital.

The EECP therapy was given as a 1-hour session, once daily, for a total of 35 sessions. The pressure applied to the cuffs was approximately 250 mm Hg. Patients were instructed to continue their optimal medical treatment for the duration of the study.

^{201}Tl-SPECT Imaging Protocol and Analysis

^{201}Tl-SPECT was performed at baseline, 1 and 6 months after EECP therapy. Exercise stress testing with use of a modified Bruce protocol as previously described was applied to eight patients [12]. In two subjects who could not exercise adequately, dipyridamole was intravenously infused to induce coronary hyperemia [13].

In the stress and delay unprocessed anterior projection image (number 9 of 32), the LHR of ^{201}Tl activity was measured using a region of interest method as previously described [9].

For analysis, the LV myocardium was divided into 17 segments as American Heart Association recommended [14]. The myocardial ^{201}Tl activity in each segment was graded on a 0- to 4-point scale. Summed scores were calculated by adding the 17 individual segment scores [15]. A summed stress score (SSS) was obtained by adding the scores of stress images. A summed rest score (SRS) was obtained similarly by adding the scores of the re-injection or redistribution images. The sum of the differences between each segment under stress and delay images was defined as the summed difference score (SDS). Two experienced observers independently interpreted the SPECT images without knowledge of patients' identity and time point. In cases of disagreement, a consensus was reached after images reviewed. Our inter-observer agreement for ^{201}Tl-SPECT interpretation was 96% ($\kappa = 0.90$, SEM = 0.079) [13].

Statistical Analysis

All enrolled patients were included for statistical analysis. Data are shown as mean ± SD. Comparisons between baseline and follow-up tests were made by use of the paired t-test for continuous variables.

Results

Patients

We studied ten CAD patients who were positive on stress myocardial perfusion imaging for ischemia despite conventional medical or surgical therapies (table 1). None of them had EECP treatment prior to this study. All subjects maintained their medication throughout the study course without change of regimen. Among them, 9 (90%) had undergone prior percutaneous coronary intervention or CABG, and 8 (80%) had a history of previous myocardial infarction. All patients showed myocardial perfusion defects on Tl-SPECT images at stress (SSS: 20.7 ± 7.5). Most of these defects persisted at rest (SRS: 13.9 ± 7.5), and only a small portion of the defects was reversible (SDS: 6.8 ± 6.0). The mean LV ejection fraction (LVEF) measured by using two-dimensional echocardiography was 56.7 ± 7.7%. All patients completed EECP therapy and received 1- and 6-month follow-up tests. No cardiovascular adverse events occurred during the study period.

^{201}Tl-SPECT Analysis

In eight patients who underwent exercise stress testing, the exercise duration before (8.2 ± 1.0 min) and after (1-month: 8.0 ± 0.6 min, p = 0.558; 6 months: 8.3 ± 1.2 min, p = 0.399) EECP treatment were not significantly different. The changes of SSS, SRS, and SDS from baseline were not statistically significant in 1- and 6-month follow-up tests (table 2). Interestingly, LHR at stress, decreased significantly from 0.40 ± 0.08 to 0.35 ± 0.08 (p = 0.001) at 1 month and the effect sustained at 6 months (0.33 ± 0.10, p = 0.03) following EECP treatment. The effect of EECP treatment on LHR at rest was not statistically significant. LVEF slightly increased from 56.7 ± 7.7% to 57.6 ± 5.9% (p = 0.382) at 1 month and to 60.1 ± 8.6% (p = 0.062) at 6 months after EECP therapy, although the improvement was not statistically significant.

Table 1. Baseline characteristics (n = 10)

Male gender	9 (90%)
Age, years	52.3 ± 5.3
Cardiac history	
Prior PCI	7 (70%)
Prior CABG	2 (20%)
Prior MI	8 (80%)
Medication	
Anti-platelet	10 (100%)
ACE inhibitor	8 (80%)
Calcium-antagonist	2 (20%)
Beta-blocker	7 (70%)
Statin	7 (70%)
Nitroglycerin	7 (70%)

ACE = Angiotensin-converting enzyme; CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Discussion

In this report, the stress LHR declined significantly at 1 and 6 months after EECP treatment. These findings suggest that the improvement of LV function after EECP may stem from the improvement of myocardial perfusion at stress [3, 4]. However, the indicator of myocardial ischemia, shown as SDS on ^{201}Tl-SPECT, did not improve significantly in this study as reported elsewhere [3, 4]. The discrepancy may originate from the high prevalence (up to 80%) of previous myocardial infarction in our study subjects, which results in large burden of scar tissue and low volume of reversible ischemic myocardium. This is supported by the relatively high SRS and low SDS at baseline.

The effects of EECP on the improvements of angina symptoms, exercise capacity, functional status, and quality of life can be maintained for at least 6 months after EECP treatment [6, 8, 16, 17]. In this reports, we documented that the reduction of stress LHR, an objective marker for the therapeutic effects of EECP, can also be maintained up to 6 months after EECP treatment [18].

It has been reported that EECP did not alter LV systolic function but improved diastolic filling [5]. Since LHR at stress correlates with LV diastolic volume and pressure [10], it is not surprising that the improvement

Table 2. ^{201}Tl SPECT analyses

	Baseline	1 month post-EECP		6 months post-EECP	
	mean ± SD	mean ± SD	p value	mean ± SD	p value
Exercise time[a], min	8.2 ± 1.0	8.0 ± 0.6	0.558	8.3 ± 1.2	0.399
SSS	20.7 ± 7.5	18.8 ± 7.1	0.121	19.9 ± 7.5	0.433
SRS	13.9 ± 7.5	14.7 ± 6.1	0.773	13.6 ± 7.6	0.890
SDS	6.8 ± 6.0	4.1 ± 3.8	0.252	6.3 ± 4.3	0.700
Stress LHR	0.40 ± 0.08	0.35 ± 0.08	0.001*	0.33 ± 0.10	0.030*
Rest LHR	0.38 ± 0.09	0.33 ± 0.05	0.061	0.36 ± 0.07	0.602
LVEF, %	56.7 ± 7.7	57.6 ± 5.9	0.382	60.1 ± 8.6	0.062

[a] Only eight patients who can perform stress exercise test are included. LHR = Lung/heart ratio; LVEF = left ventricular ejection fraction; SDS = summed difference score; SRS = summed rest score; SSS = summed stress score; * p < 0.05 when compared with baseline.

of LHR at stress after EECP treatment did not accompany with a significant improvement of LVEF in this study.

The majority (90%) of patients included in this clinical study have prior percutaneous coronary intervention or CABG, or both. Thus, although the study is relatively small in sample size, it does represent one of the applications of EECP in the real world, i.e., for the treatment of patients with CAD that have been refractory to conventional interventional approaches.

There are several limitations in this study. First of all, the statistic power is limited by the small sample size, which may cause the improvement of LV systolic function at 6 months after EECP be marginal. Second, there is no control group. Although it is technically difficult to conduct a double-blind, placebo-controlled study for EECP, a larger, randomized study with parallel control group will be helpful to confirm the efficacy of EECP treatment.

Conclusion

EECP improved LV function, shown as the reduction of LHR at stress, in patients with CAD. For long-term beneficial effects on LV systolic function, a large-scale study with repeat augmentation may be indicated.

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