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Research Article

# Enhanced External Counterpulsation Can Improve Neutrophil to Lymphocyte Ratio in Patients with Chronic Heart Failure

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**Abstract**

**Background:** External enhanced Counterpulsation (EECP) is a non-invasive Counterpulsation technique which uses three sets of pneumatic cuffs fasten around the lower extremis. EECP improve coronary perfusion and left ventricle systolic unloading and increase nitric oxide (NO) plasma level which is a vasodilator, anti-thrombotic and anti-inflammatory factor and improve vascular function. In other hand the relation between WBC count, N/L ratio (neutrophil to lymphocyte) and cardiovascular disease had been proved before and demonstrated inflammatory conditions predict long-term mortality in patients with heart failure. The purpose of this study is to evaluate effect of Enhanced external Counterpulsation intervention on noeutrophil-lymphocyte ratio.

**Methods:** Three pairs of EECP compression cuffs devices were fastened at the hips, thighs, legs. Control and ECG monitoring for an hour during 35 sessions period of EECP, all demographic data, underlying diseases (diabetes, chronic kidney disease, etc.), and the dosage and type of medications have been recorded in the checklist before and after the EECP treatment, Complete Blood Count (CBC) has been conducted and the results were recorded on the data collecting form.

**Results:** After intervention WBCs and neutrophil counts reduced with signicant correlation, Lympcytes level increase after EECP intervention. N/R ratio decreased from mean 2.172 ± 0.446 to 1.874 ± 0.342 after EECP with significant correlation (P = 0.0001).

**Conclusion:** EECP treatment had a positive role in inflammatory condition which reduce N/L ratio as an inflammatory index which has an important factor show long-term mortality in patients with heart failure.

**Keywords:** Enhanced external Counterpulsation; EECP; HF; Heart Failure; Neutrophil to Lymphocyte Ratio; N/L Ratio

## Abbreviations

EECP: Enhanced External Counterpulsation; IHD: Ischemic Heart Disease; IABP: Intra-aortic Balloon Pumping; CCS: Cardiovascular Society Classification; NO: Nitric Oxide; Hb: hemoglobin; N/L: Neutrophil to Lymphocyte; Cluster differentiation: CD4/CD8; WBC: White Blood Cell; CABG: Coronary Artery Bypass Grafting; CHF: Chronic Heart Failure; CAD: Coronary Artery Disease; PTCA: Percutaneous Transluminal Coronary Angioplasty; CBC: Complete Blood Count

## Introduction

Enhanced external Counterpulsation (EECP) is a non-invasive Counterpulsation technique, which uses three sets of pneumatic cuffs fasten around the lower limbs with FDA-approved treatment for patients with Ischemic Heart Disease (IHD) but not for heart failure [1]. The cuffs are inflated tandemly at the first of diastole, producing aortic counter pulsation, diastolic augmentation, and increased venous return. At the first of systole, the external pressure in the cuffs is released, producing a decrease in systolic pressure. The hemodynamic effects are similar to intra-aortic balloon pumping (IABP) that is an invasive method that increase coronary blood flow [2]. In contrast to IABP which is an invasive method, EECP increase in coronary blood flow noninvasively [3]. A treatment procedure includes 1 to 2 hours/day for a total 35 session of therapy. Several studies have shown patient improvement with lowering in Canadian Cardiovascular Society Classification (CCS) [4]. From theatrical view the patients with heart failure were initially excluded from studies because of exacerbation risk of heart failure that felt increase in venous return, and this might overload the weakened left ventricle or precipitate ischemia by increasing stress on the ventricle wall. However experimental studies show increase coronary perfusion, increased intrinsic myocardial contractility, improved left ventricular diastolic pressure and decreased cardiac work after EECP [5]. EECP improve coronary perfusion and left ventricle systolic unloading, but it is not clear that EECP has long-term benefit [6]. EECP increase nitric oxide (NO) plasma level which is a vasodilator, anti-thrombotic and anti-inflammatory factor that improve vascular function [7]. In other hand the relation between White Blood Cell (WBC) count, Neutrophil to Lymphocyte ( N/L) ratio and cardiovascular




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disease had been proved in many studies [8]. N/L ratio is one of the factors that show existence of inflammation and indicate activity of inflammation system in the body that are subtypes of WBC which change in cardiovascular disease, and patients with heart failure [9]. This inflammatory factor indicates arthrosclerosis progression in micro vascular [10]. Interactions between neutrophils and platelets cause this inflammation progress and plugging in micro vascular [11]. In additional lymphocyte counts reduce in inflammation situation increasing of corticosteroids that cause change in lymphocytes and CD4/CD8 (Cluster differentiation) ratio [12]. These mechanical changes increase mortality among patients with heart failure in acute phase [13]. A study of Arruda-Olsen et al indicates relation between increase in neutophil count and long term mortality in patients with heart failure [10]. A study of Cho KH showed accompanying hemoglobin (Hb) and N/L ratio can predict mortality rate in patients with acute coronary phase in future 6 months [14]. In other study N/L Ratio impute as an inexpensive and effective factor of prediction of patients mortality in acute Heart Failure [15,16]. So we use N/L ratio as a trusty factor in this study [17]. The aim of this study is to show if EECP procedures can effect on N/L ratio and the mount of WBC in patients with heart failure and if EECP procedures can effect on neutrophils and lymphocytes counts. The purpose of this study is to evaluate effect of EECP intervention on noeutrophil-lymphocyte ratio.

## Methods

The type of this study was before and after intervention analysis without the control group. The study was conducted on patients referred to the department of physical medicine and rehabilitation of Shahid Madani Hospital of Tabriz University of medical science. Convenient sampling method (available) was census. So that, all heart failure patients who met the criteria were enrolled in the study after obtaining written informed consent. 33 patients were included during the study period. Data was developed in checklist by the researcher. The study design was approved by the ethics committee of Tabriz University of Medical science (TUMS). The Patients gave a written consent to be enrolled in the study and also to make use of their medical file data. Inclusion criteria consist of Non-ischemic Chronic Heart Failure (CHF) patients with inappropriate response to maximum doses of medication, CHF patients with Coronary Artery Disease (CAD) who are not suitable for Coronary Artery Bypass Grafting (CABG) and Percutaneous Transluminal Coronary Angioplasty (PTCA) and with inappropriate response to a maximum dose of medication. Exclusion criteria consist of arrhythmia leading to impaired function of instrument, history of bleeding tendency or use of anticoagulant, active thrombophlebitis of extremities, a proofed aortic aneurysm with the need for surgical intervention and pregnancy and patients with significant (moderate to severe) valvular disease on the left side of the heart. After determining the functional class by Canadian cardiovascular society (CCS) and adjusting the patient's medications by cardiologist, patients were referred to Physical Medicine and Rehabilitation department. First of all, demographic data, underlying diseases (diabetes, chronic kidney disease etc.), and the type of dosage and medication, was recorded in the checklist. Before starting the EECP treatment, Complete Blood Count (CBC) has been conducted and the results were recorded on the data collecting form. Then by the relevant expert and permanent monitoring of physiotherapist, three pairs of EECP compression cuffs devices were fastened at the hips, thighs and legs, the cuffs were filled during diastolic time, facilitating venous return and were unloaded at the beginning of systolic time. The rhythmic deflation and inflation were continued by ECG monitoring for an hour. During this period that consists of 35 sessions, patients were visited by a cardiologist for several times. All data were recorded on the checklist before and after the completion of EECP, including CBC. All complications and unpleasant events (like MI hospitalization and skin conditions etc.) were recorded during treatment.

**Table 1:** Comparisson of inflammatory factors before and after the EECP treatment (with CI=95%).

| | Before intervention(Mean ± SD) | After intervention(Mean ± SD) | P-Value |
|---|---|---|---|
| WBC | 6.95 ± 1.46 | 6.58 ± 1.11 | 0.001 |
| N/L Ratio | 2.15 ± 0.45 | 1.85 ± 0.36 | 0.001 |
| Neutrophil | 4.46 ± 1.06 | 3.97 ± 0.74 | 1E-04 |
| lymphocyte | 2.11 ± 0.47 | 2.17 ± 0.41 | 0.01 |

**Table 2:** Comparisson of effect of EECP on N/L Ratio. The numbers express patients.

| | N/L ratio<2 | 3>N/L ratio≥2 | N/L ratio≥3 |
|---|---|---|---|
| N/L Ratio before EECP | 12 (38.7% ) | 17 (54.8%) | 2(6.5 %) |
| N/L Ratio after EECP | 25(80.6%) | 6(19.4%) | 0 |

### Statistical methods

Collected data was analyzed by SPSS version 16 software and the results were reported as Mean ± SD. To compare the quantitative changes, Paired samples T-test was used. In this study, the confidence interval was 95% and P-value less than 0/05 was considered significant.

## Results

A total of 33 Heart Failure subjects were referred to EECP intervention ward during 2 year in the present study. The mean age of the subjects were 60/8 ± 8/6 ranging from 45 to 77 years. The percentage of males and female were 74.2% and 25.8% respectively. Two subjects had history of MI with Ejection Fraction (EF) less than 40% (EF< 40%) excluded due to further MI and end stage heart failure during this study. These subjects were excluded from the final analysis. In this study, there were 14 patients (45.2%) with a history of IHD, 18 patients (58.1%) with a history of Hypertension (HTN), 13 patients (41.9%) with a history of Diabetes Mellitus (DM), 17 patients with a history of Hyperlipidemia (54.8%), 3 patients (9.7%) with a history of Chronic Renal Failure (CRF), 11 patients (35.5%) with a history of smoking and 4 (12.9%) patients with a history of obesity. 1 patient (3.2%) with a history of unstable angina. WBCs, neutrophils, lymphocytes and N/L Ratio are measured before and after the 35 sessions of EECP period and compared. Our results ( Table 1) demonstrate that plasma level of WBCs reduce (from mean 6.95 ± 1.46 to 6.58 ± 1.11 ) after EECP intervention with signicant correlation (P = 0.001) and Neutrophils level reduced (from mean 4.46 ± 1.06 to 3.97 ± 0.73) after EECP intervention with signicant correlation (P = 0.0001), Lympcytes level increase (mean 2.10 ± 0.47 to 2.17 ± 0.41 ) after EECP intervention with significant correlation (P = 0.010) and we calculate N/R ratio that decrease (from mean 2.17 ± 0.45 to 1.87 ± 0.34) after EECP with significant correlation (P = 0.0001). In other words N/L ratio was up to 3 (N/L ratio ≥3) in 2

patients ( 6.5%), 17 patients (54.8%) was between 2 and 3 (3 >N/L ratio ≥2) and 12 (38.7% ) patients was lower than 2 (N/L ratio<2 ), after EECP treatment no patient was up to 3 (0%), 6 (19.4%) was between 2 and 3 (3 >N/L ratio ≥2) and 25 patients was lower than 2 (N/L ratio <2 ) ( Table 2).

## Discussion

Our study demonstrated that there is a relation between EECP intervention and N/L Ratio. Neutrophil counts are activator factors of inflammation and can predict cardiovascular mortality [18], that infiltrate near the fibrous cap and obstruct the small vessels [19,20]. Arruda et al demonstrated the relation between increase in neutrophil counts and increase in heart failure incidences and long-term mortality in patients with Myocardial Infarction (MI) (10). Also demonstrated that activated netrophils released inflammatory factors such as myeloperoxidase and elastase which cause tissues destruction, increase in inflammation condition like heart failure [21]. In other hand in some studies lymphocytopenia counted as an important marker that increase mortality in patients with heart failure [21,22]. N/L ratio described as an another important and inexpensive factor that could predict mortality [16]. Improved endothelial function can reduce mortality and morbidity in patients with heart failure [23]. EECP is a FDA-approved intervention for CAD and IHD but not for heart failure, improved peripheral vascular and endothelial function [1-5]. The EECP assessment in chronic heart failure is very limited comparing with myocardial ischemia; since Earlier patients with chronic heart failure were excluded from the study due to the Theoretical risk of increased overloading of left ventricle resulting from increase in venous return or worsening ischemia for increasing stress of ventricular wall [24], Although empirical studies later demonstrated increase in coronary perfusion, contractility and improvement in ventricular diastolic pressure and heart function after EECP intervention [25]. Also it has been reported that exercise tolerance improved in patients with chronic heart failure [26]. However, all studies did not confirm this result [27]. Hence we use N/L ratio as an important factor to estimate inflammatory conditions in our subjects before and after EECP intervention. After it neutrophil counts and WBCs reduced significantly, lymphocyte counts increased after EECP intervention and finally N/L ratio reduced significantly that demonstrated a better inflammatory condition after EECP intervention. These results demonstrated that EECP intervention can improve inflammatory condition in patients with heart failure. Arbel et al [28] divided N/L ratio in 3 groups, up to 3 (N/L ratio ≥3), between 2&3 (3 >N/L ratio ≥2) and lower than (N/L ratio <2) and demonstrated positive correlation between increase in N/L value and coronary artery disease (CAD) severity and a higher risk for patients with N/L value up to 3. In this study After EECP treatment, N/L value improved from %6.5 (N/L ratio ≥3) to zero. In lower value in our subjects, inflammatory condition reduced (in 3 >N/L ratio ≥2) from %54.8 to %19.4 and more values led to lower than 2 (N/L ratio <2). This reduction also confirmed positive effect of EECP intervention on N/L ratio as an inflammatory factor. There are a few studies about positive effect of EECP on heart failure [29,30]. And there is not much study that show if EECP improve heart failure prognosis in short-term and affect on mortality in patients with heart failure or not. We suggest that more study will be done to demonstrate benefits of EECP intervention in heart failure treatment.

## Conclusion

We discovered that EECP intervention can reduce N/L ratio as an inflammatory index which has an important factor to predict long-term mortality in patients with heart failure.

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