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Effects of Enhanced External Counterpulsation (EECP) on Myocardial Perfusion

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Purpose: To evaluate whether enhanced external counterpulsation (EECP) exerts an effect on myocardial perfusion.

Methods: Eleven patients with angina were studied before and after 35 sessions of EECP treatment. Myocardial perfusion was quantified with positron emission tomography and intravenous 13N-ammonia at rest and after dipyridamole, by means of a two-compartment mathematical model.

Conclusion: The results suggest that EECP has no effect on myocardial perfusion. However, because of the small number of patients in this study and highly variable clinical responses, additional studies are required to corroborate this finding. The beneficial effects of EECP appear to be mediated by other mechanisms.

Keywords: Enhanced External Counterpulsation, myocardial perfusion

INTRODUCTION

Prior open and multicenter randomized controlled clinical trials of Enhanced External Counterpulsation (EECP) have demonstrated a number of clinical benefits for patients with refractory angina, despite prior revascularization attempts and treatment with multidrug regimens.[1–7]

EECP is a noninvasive technique that involves placement of a series of three pressure cuffs around the legs and buttocks. Air is introduced into the cuffs, which then sequentially compress the calves, lower thighs, and upper thighs (distal to proximal). The intended therapeutic action is for increased blood flow and blood pressure to reach coronary vessels at the time of lowest intramyocardial tension.

Results from these trials have demonstrated increased exercise duration on treadmill testing, increased time to ST-segment depression, and decreased numbers of anginal episodes following completion of 35 sessions of active EECP treatment in patients with coronary artery disease (CAD).[1–7]

Although there is clinical evidence that EECP has an anti-ischemic effect, the responsible mode of action has not been determined. One hypothesized mechanism is the enhancement of myocardial perfusion with use of conventional scintigraphic approaches. This enhanced perfusion may then facilitate collateral flow to promote anginal symptom relief.

This study was conducted to determine whether EECP exerts an effect on quantitative estimates of myocardial perfusion, by measurement of myocardial blood flow with dynamic positron emission tomography (PET) before and after EECP treatment.

METHODS

Patients

Eleven (23%) of 47 consecutive patients with CAD were recruited to participate in this study of myocardial perfusion. All patients were randomized to receive 35 sessions of active EECP treatment. The institutional

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review board approved this study, and informed consent was obtained from each subject.

Criteria for enrollment were from the multicenter study of EECP (MUST-EECP)[1]: 23 to 82 years of age; Canadian Cardiovascular Society Class I, II, or III; evidence of CAD by one of three measures [angiographic-proven disease of >1 major coronary artery (luminal stenosis >70% in at least one view of an angiogram), documented enzymatic and/or electrocardiographic evidence of myocardial infarction (MI), or positive nuclear exercise stress test for MI and/or ischemia]; and positive exercise stress test, defined as ischemic type (horizontal or downsloping) ST segment depression >1 mm, occurring 80 msec after the J point and persisting for at least three consecutive beats.

Patients were excluded if they were pregnant or of child-bearing potential and not using a contraceptive method; presented with unstable angina, arrhythmias, or marked electrocardiographic abnormalities that would interfere with triggering of EECP or endpoint interpretations; had had MI or coronary artery bypass surgery in the previous 3 months; had undergone cardiac catheterization in the previous 2 weeks; had a permanent pacemaker or implantable defibrillator; were currently enrolled in a cardiac rehabilitation program; or had any of the following: overt congestive heart failure (left ventricular ejection fraction <30%); significant valvular heart disease; severe symptomatic peripheral vascular disease, history of varicosities, deep vein thrombosis, phlebitis, and/or stasis ulcer; arterial blood pressure >180/110 mm Hg; bleeding diathesis; warfarin use with international normalized ratio >2.0; inability to undergo treadmill testing; or nonbypassed left main disease >50%.

EECP treatment procedures

Patients underwent EECP in 1-hour sessions for a total of 35 treatments. Patients had 1 or 2 treatments per day, 5 days per week, according to their preference. The 35 sessions required for completion of treatment occurred over a period of 4 to 7 weeks.

Dynamic PET procedures

PET imaging was performed on a whole-body tomograph in 11 patients randomized to receive EECP treatment. Cardiac medications were continued as prescribed and unchanged during the course of treatment. Subjects were studied after an overnight fast. All beverages, foods, and medicines containing methylxanthines (e.g., caffeine) were withheld for at least 24 hours before the PET study. An ECAT Exact-47 whole-body PET scanner (Siemens/CTI, Knoxville, TN) was used and provided 47 transaxial slices. The heart was centered in the field of view during a 2-minute transmission scan with use of the rotating rod source of germanium-68/gallium-68. The torso was then marked with indelible ink, and the body position was checked frequently with laser coregistration. A 15- to 20-minute transmission scan was performed to correct for attenuation.

For measurement of myocardial perfusion, 10–20 mCi of nitrogen-^{13}N ammonia was administered intravenously over 30 seconds with a constant-infusion pump. Dynamic imaging was performed for a total of 19 minutes, starting just prior to the start of tracer administration (twelve 10-second frames, two 30-second frames, one 60-second frame, and one 90-second frame). After completion of the rest study, radioactivity was allowed to decay to background levels and then dipyridamole (0.56 mg/kg) was infused over 4 minutes. Blood pressure and the electrocardiogram were recorded every minute during the dipyridamole infusion. Four minutes after the end of the infusion, a second dose of ^{13}N-ammonia was administered and the sequential dynamic imaging sequence was repeated.

Image analysis

The transaxial images were reoriented into short axis projections for analysis. Images were reconstructed with a HANN filter with a critical frequency of 0.4 cycles per pixel, giving a reconstructed spatial resolution of 10 mm in both the x and y axes. The last frame was used for placement of regions of interest on each short axis slice, which was divided into eight equal sectors subtending 45 degrees. In addition, multiple regions of interest were placed in the center of the left ventricular blood pool in the most basal slices and averaged to comprise the input function, necessary for computation of myocardial perfusion. Regions of interest were then copied onto the initial 120 seconds of data images, and counts in the blood and myocardial region input were put into a two-compartment model for measurement of myocardial perfusion in each region. Correction for conversion of tracer to metabolites was not made because data analysis was limited to the first 120 seconds, during which conversion of ammonia to metabolites is negligible. Myocardial perfusion was determined in 4 to 8 short-axis slices in each patient, so there were typically 32 to 64 regions of interest per subject.[8–10]

Perfusion analysis

Myocardial regions were divided into those that appeared mostly normal and those that appeared to be either infracted (activity at rest <50% of maximum, which did not change with stress) or ischemic (ie, those

with a stress-induced decrease in counts in comparison with rest).

Adverse events

At each treatment session, patients were asked to comment on any side effects or adverse events experienced over the previous 24 hours. Patients were asked to report any leg discomfort, arrhythmias, or angina. All events were reported to a core laboratory within 24 hours to guarantee the safety of patients.

Evaluation of hemodynamic effects

Heart rate and systolic and diastolic blood pressure were determined <4 weeks prior to treatment initiation and <2 weeks after completion of all 35 treatment sessions.

Statistical analysis

Baseline demographic and clinical characteristics were evaluated with the use of descriptive statistics. Data were expressed as mean ± SD or as a percentage of the total patient population. Tests of statistical significance for all end points were determined with the sign test. A separate subanalysis was conducted on the correlation of improved myocardial perfusion with or without dipyridamole in infracted/ischemic versus noninfarcted zones by clinical improvement for each endpoint investigated in this study. All tests of statistical significance were two-sided with an α level of .05.

RESULTS

Efficacy and safety

In this patient group there was a nonstatistically significant trend toward improvement in only two of four efficacy endpoints. The mean number of reported anginal episodes during exercise decreased from 1.8 ± 3.9/day after the first three EECP treatments to 0.5 ± 0.8/day after the last three EECP treatments. Oral nitroglycerin use also declined from a mean 1.27 ± 3.58 tablets/day after the first three EECP treatments to a mean 0.09 ± 0.30 tablets/day after the last three EECP treatments. However, only 4 patients (36%) had fewer anginal episodes and only 3 (27%) used fewer nitroglycerines in the total sample.

Mean exercise duration decreased slightly, from 366 ± 151 seconds at baseline to 349 ± 223 seconds post-treatment. Mean time to ST-segment depression also declined slightly, from 257 ± 182 seconds at baseline to 207 ± 179 seconds post-treatment. Only 5 patients (45%) demonstrated improvement in exercise duration, and only 2 (18%) showed improvement in time to ST-segment depression.

Adverse events during EECP treatment were minimal (Table 3). Three patients reported an episode of leg discomfort. Several patients had arrhythmias; however, these episodes were attributed to refractory CAD and not necessarily related to EECP treatment.

Myocardial perfusion

There were a total of 80 regions of interest analyzed. Fifty-one regions appeared to be mostly normal (nonischemic), 26 were believed to reflect reversible ischemia, and the remaining 3 segments were designated as infarcted. The infarcted zones were excluded from further analysis. In the regions believed to be mostly normal, myocardial perfusion prior to EECP averaged 96 ± 19 mL/100 g/min and increased after dipyridamole to 168 ± 77 mL/100 g/min. Perfusion in these regions were not affected by EECP (68 ± 20 mL/100 g/min at rest and 165 ± 66 mL/g/min after dipyridamole). Myocardial perfusion in regions believed to be ischemic was diminished in comparison with regions believed to be mostly normal. Prior to EECP, myocardial perfusion in the ischemic regions averaged 80 ± 15 mL/100 g/min and increased only minimally after dipyridamole (flow 99 ± 50 mL/100 g/min). Myocardial perfusion in these regions was not affected by EECP (61 ± 35 and 77 ± 60 mL/100 g/min at rest and after dipyridamole, respectively).

Patient profile

The majority of patients were Caucasian males (Table 1). Mean age was 63 years, and the mean duration of an angina diagnosis was almost 4 years. All patients had a prior catheterization, which demonstrated at least one occluded artery in the majority the them, despite prior revascularization attempts (Table 2). Most patients had a history of MI and were undergoing treatment with a multidrug regimen consisting of nitrates and a β-blocker and/or calcium channel blocker.

Table 1. Characteristics of the patients (n = 11).

Characteristic	Value
Age, mean, years (SD)	63 (11)
Angina duration, mean, years (SD)	4 (2)
Male, n (%)	10 (91)
Race, n (%)	
Caucasian	9 (82%)
African-American	1 (9%)
Other	1 (9%)

Table 2. Cardiovascular profiles (n = 11).

Variable	No. (%) of patients
Family history of coronary artery disease	5 (46%)
Prior angioplasty	2 (18%)
Prior coronary artery bypass grafting	4 (36%)
Prior catheterization	11 (100%)
Prior myocardial infarction	8 (73%)
Number of occluded vessels	
1	1 (9%)
2	0 (0%)
3	1 (9%)
Prescribed drug therapy	
β-Blocker	6 (55%)
Calcium channel blocker	6 (55%)
Nitrates	10 (91%)
Prescribed multidrug regimen	
Two-drug	8 (73%)
Three-drug	2 (18%)

Hemodynamic effects

In terms of hemodynamic effects of EECP treatment, statistically significant increases in mean heart rate (58 ± 18 to 61 ± 15 beats per minute) and clinically and statistically nonsignificant reductions in mean systolic blood pressure (139 ± 25 to 132 ± 19 mm Hg) and diastolic blood pressure (74 ± 11 to 73 ± 14 mm Hg) were noted from baseline to posttreatment.

DISCUSSION

Although previous work by others has demonstrated an increase in perfusion in zones with diminished perfusion prior to EECP, we did not corroborate this in the present study. The previous studies were generally performed with planar thallium scan analysis, except for a single-center study, and did not provide detailed regional information or quantitative data. In contrast, PET provides absolute estimates of myocardial perfusion and corrects for attenuation. However, the number of patients who improved either subjectively or objectively was small in our study, and patients who have more marked functional or physiological effects from EECP may in fact have alteration in myocardial perfusion.

Table 3. Adverse events during enhanced external counterpulsation (EECP) treatment (n = 11).

Event, no. of episodes	No. (%) of patients
Arrhythmia	
1	2 (18%)
2–5	1 (9%)
>5	2 (18%)
Leg discomfort	
1	2 (27%)

The patients in our study all had substantial CAD. Even in the mostly normal-perfusion vascular territories, myocardial perfusion only doubled in response to dipyridamole, rather than the usual 3- to 4-fold response observed in normal vessels. The results of the study suggested that EECP may not alter myocardial perfusion, and that the beneficial effects of EECP seen are likely related to effects other than alteration in myocardial perfusion.

This study was limited by the inclusion of fewer than 50% of patients responding favorably to EECP by each clinical endpoint, and a response rate of only 18% for any objective measurement. In addition, there may have been a potential for selection bias, because only 23% of total patients enrolled at the center were included. Inclusion of a larger study population would have improved the power to adequately test all four endpoints for myocardial perfusion and specifically test improvement in myocardial perfusion in nonischemic zones at rest. Selection bias may also have effected the lack of clinical and perfusion improvement in these patients.

In summary, in this study, EECP did not alter myocardial perfusion in either normal or ischemic regions.

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