Psychosocial Effects of Enhanced External Counterpulsation in the Angina Patient: A Second Study

SUSAN SPRINGER, M.D., ALISON FIFE, M.D., M.P.H.
WILLIAM LAWSON, M.D., JOHN C.K. HUI, PH.D.
LINA JANDORF, M.A., PETER F. COHN, M.D.
GREGORY FRICCHIONE, M.D.

Enhanced external counterpulsation (EECP) is a noninvasive technique that has shown promise in the treatment of ischemic coronary artery disease. Patients undergoing EECP were tested for alterations in psychosocial state associated with treatment. Overall perception of health and quality of life improved with EECP. There was also significant improvement in levels of depression, anxiety, and somatization but no change in levels of anger or hostility. On most measures, change was more significant for subjects who showed objective evidence of resolution of ischemia. Given the known predictive relationship between depression and mortality from cardiac disease, the improvement in depression scores through EECP indicates a finding of potential importance that may warrant further study in future research. (Psychosomatics 2001; 42:124–132)

Psychiatric states of depression,[1–5] anger,[6] and anxiety[3,7] and the psychosocial and environmental triggers of acute and chronic stress[8,9] have been shown in recent studies to be associated with myocardial ischemia[8–10] and also with increased morbidity and mortality from cardiac events[1–6,9] in patients with coronary artery disease (CAD). Ischemia is often experienced by the patient as anginal pain.[12,13] Refractory angina, in which pain continues to occur even after medication and surgical remedies have been optimized, can worsen a patient's functional disability and lead to heightened negative emotional arousal states of stress, anxiety, anger, and depression. Potentially, these negative states, if allowed to persist, may adversely impact morbidity and mortality, and quality of life. Myocardial ischemia and cardiac mortality and morbidity can be lowered in patients with refractory angina by a noninvasive treatment called enhanced external counterpulsation (EECP),[14–25] which is described in more detail below. A previous study postulated that EECP may also have significant psychosocial effects.[26,27] If EECP can be shown to significantly reduce levels of depression, anxiety, anger, and psychosocial stress or increase quality of life, this finding may represent an additional benefit of the therapy.

This study is a follow-up study to test for such psychosocial effects. In a previous study, Fricchione et al.[26] found that patients experienced significant subjective improvement in refractory angina as indicated by reduced use of nitrates and decreased severity and frequency of angina. A majority of patients reported significant improvement in their quality of life. Even patients with ischemic heart disease, objectively unchanged on thallium scan after EECP, were found to rate overall well-being as improved, sug-

Received April 27, 2000; revised September 7, 2000; accepted November 27, 2000. From the Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts; Department of Psychiatry, Brigham and Women's Hospital, Boston, Massachusetts; Department of Medicine, Division of Cardiology, SUNY at Stony Brook; Department of Surgery, SUNY at Stony Brook; Ruttenberg Cancer Center, Mount Sinai School of Medicine, New York City; The Carter Center, Atlanta, Georgia; Harvard Medical School, Boston, Massachusetts. Address correspondence and reprint requests to Dr. Springer, Department of Psychiatry/WAC 812, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114–2696.

gesting the possibility of a psychosocial benefit of EECP and raising the question of whether the technological intervention of EECP may directly impact on depressed mood and levels of anxiety or anger.

The purpose of the present study is to analyze the psychosocial effects of EECP in greater depth and with a larger sample size than the previous study. Several specific questions are posed. First, are the results of this study consistent with earlier findings that EECP treatment is associated with significant subjective improvement in refractory angina? Second, is a course of EECP therapy associated with significant alteration in patient levels of depression, anxiety, hostility, anger, somatization, and general psychological distress? Third, are psychosocial alterations consistent between the subset of patients whose physiologic state shows objective evidence of partially resolved myocardial ischemia on thallium imagery after EECP and the subset who have no change in ischemia? Fourth, is EECP treatment well tolerated psychologically and socially as indicated on measures of quality of life? Fifth, do any pretest psychosocial variables have significant association with the degree to which patients respond to EECP therapy with physiologic improvement of ischemia? If so, selection criteria for candidates for EECP treatment could be expanded to include psychological pretesting.

METHODS

EECP is a noninvasive treatment for angina pectoris. During EECP therapy, external pneumatic pantaloons on calves, thighs, and buttocks pulse sequentially, from distal to proximal, in precise synchronization with heart rate on an electrocardiogram, to provide diastolic augmentation, thus increasing preload, cardiac output, and diastolic aortic retrograde flow, while decreasing systolic pressure, afterload, and cardiac work.[20] Diastolic augmentation generates increased coronary artery perfusion during diastole, which may contribute to lowering myocardial ischemia. Studies suggest that increased perfusion may promote lasting coronary artery collateral revascularization leading to symptom reduction and increased survival. EECP treatments last 1–2 hours during which time the patient is on a couch, strapped to a rhythmically thumping, pulsing, and undulating apparatus. A standard course of 35 hours of EECP therapy is given weekdays for approximately 7 weeks.

Male patients with a diagnosis of angina refractory to medical or surgical intervention were consecutively enrolled for this study. All patients had CAD documented by cardiac catheterization and reversible perfusion defects on stress thallium imagery. Criteria for exclusion included a recent myocardial infarction (MI)(within the past 3 months), clinical congestive heart failure, aortic insufficiency, uncontrolled hypertension (>180/110 mmHg), significant ventricular arrhythmias, atrial fibrillation, severe peripheral arterial or venous disease, nonischemic cardiomyopathy, or bleeding diathesis. Forty patients were admitted into the Human Research Committee-approved EECP protocol of the State University of New York (SUNY) at Stony Brook after informed consent.

Prior to treatment, all patients had a stress radionuclide scan and an exercise tolerance tests (ETT) with standard Bruce Protocol limited by symptoms. After the course of EECP, patients underwent a repeat stress thallium test for the same duration as pretreatment and a symptom-limited maximal ETT. One day prior to EECP, each patient completed a questionnaire on the severity and frequency of angina and use of anti-anginal medications—Subjective Pain and Disability Assessment (SPDA) and a battery of four psychological tests. These tests included the General Health Quality Index (GHQ),[28,29] a numeric indicator representing the overall effects of illness on psychosocial function; Spielberger's State and Trait Anxiety Indices (STAI),[30,31] which rate the "state" or "trait" levels of anxiety and anger in four indices; the Beck Depression Inventory (BDI),[32] which measures level of depression; and the Symptom Check-List 90-Revised (SCL-90-R)[33] which derives two indices, a symptom total, and a set of subscales based on weighted responses to 90 items of psychological or somatic symptoms of distress. On the last day of testing, each patient again completed the SPDA and four psychological tests and in addition gave a subjective report of the changes they had experienced in quality of life (QOL) after a course of EECP.

Twenty-eight patients completed testing both before and after conclusion of EECP. Of these, 27 patients submitted SPDA and QOL questionnaires, and 26, 22, 25, and 21 patients completed the GHQ, STAI, BDI, and SCL respectively. Twelve additional patients completed questionnaires only before EECP, and this set of data was reserved solely for statistical analyses on the fifth question, the effects of pretest psychological state on post-EECP resolution of ischemia.

First, data were analyzed for the null hypothesis of equal variances among comparable data sets of each variable, with a cutoff for statistical significance of Prob>F of 0.05. If the Prob>F≤0.05, the paired *t*-test for data sets with unequal variances was calculated; if the Prob>F>0.05, the paired *t*-test for data sets with equal

variances was calculated. Paired *t*-tests with the null hypothesis of equal means across data sets were calculated with a cutoff for statistical significance of Prob>[t] of 0.05.

We analyzed data on depression more closely. In two previous studies[1,2] where the level of depressive symptoms was found to be an independent risk factor for mortality after MI, in measuring that effect, regression analyses were run by dichotomizing the BDI, using a cutoff of BDI>10 (mild to moderate symptoms of depression) to represent the presence of a depressed state. In the present study, data on baseline mean level of depression in patients will be included and will be made comparable with the previous studies by dichotomizing them at the BDI>10 versus BDI≤10 cutoff and then examining alterations in the BDI before and after EECP as well as the difference in means.

RESULTS

To provide the data set for analysis to answer the first four questions of the study, 28 male patients were enrolled [mean ± standard deviation (SD) = 63.57 ± 7.88; range = 46–75], and 27 out of 28 completed the EECP protocol. Seventeen of 27 patients (63.0%) were categorized as "Improved" myocardial perfusion on stress thallium imagery post EECP in that reversible defects were resolved, and 10 of 27 (37.0%) had "Unchanged" perfusion scans. In Table 1, patient responses to the SPDA questionnaire are shown. Patients' angina frequency, angina severity, and use of antianginal medication all decreased significantly after the completion of a course of EECP. Overall, patients note a decrease in the frequency of angina from a mean of 3.5 to 1.3 times/week, with a corresponding drop in use of nitrates from 3.3 to 0.7 times/week. Mean levels of chest pain severity lessen from 2.4 to 1.7. All decreases are highly significant at $P<0.0001$.

Symptoms significantly decreased whether the patients' ischemia resolved or remained unchanged. The level of significance is higher for patients whose ischemia improved, at $P<0.001$, but it is possible that that finding may, in part, represent a statistical effect of the difference in sample size. Interestingly, mean levels of all anginal characteristics were higher before EECP therapy for patients with ischemia that remained Unchanged after EECP than for patients whose ischemia Improved. These patients have notably higher mean levels of chest pain frequency (4.2 ± 2.9 vs. 3.1 ± 2.7) and nitrate use frequency (4.0 ± 3.1 vs. 2.9 ± 2.7). Ischemia Improved patients drop to less than a quarter of their pretreatment frequency of chest pain or nitrate use with EECP, while patients with ischemia Unchanged drop to approximately one-half the pretreatment frequency. Mean levels of all indicators of SPDA remain elevated for those with Unchanged angina relative to those with Improved angina, although levels are below the level at which even the Improved group started out. No patient in this study reported a higher level of pain or nitrate use after EECP.

Table 2 represents findings on the psychological tests taken before and after EECP treatment. A positive difference of means in an indicator represents amelioration of the psychological state; the more positive the difference, the greater the decrease in negative symptoms after a course of EECP. EECP treatment is associated with multiple significant psychosocial effects. All statistically significant psychosocial effects are in the direction of amelioration.

Several of the measures that indicate general psychosocial state show amelioration for the total sample of patients after EECP. GHQ, the measure of psychosocial function in the context of illness, is significantly higher for the total sample of patients after a course of EECP (4.33 ± 1.13, $P<0.001$). When broken down into patients who show Improved perfusion after EECP and patients

TABLE 1. Subjective pain and disability assessment before and after enhanced external counterpulsation (EECP), *N* = 27

	n	Pre EECP Mean ± SD	Post EECP Mean ± SD	*P* Value[a]
Chest pain frequency per week		3.5 ± 2.8	1.3 ± 1.7	<0.0001
Ischemia improved	17	3.1 ± 2.7	0.7 ± 0.8	<0.01
Ischemia unchanged	10	4.2 ± 2.9	2.2 ± 2.4	<0.05
Chest pain severity (scale 1–4)		2.4 ± 1.0	1.7 ± 0.7	<0.0001
Ischemia improved	17	2.4 ± 1.0	1.5 ± 0.6	<0.01
Ischemia unchanged	10	2.6 ± 1.1	1.9 ± 0.9	<0.05
Nitrate use frequency per week		3.3 ± 2.9	0.7 ± 1.3	<0.001
Ischemia improved	17	2.9 ± 2.7	0.4 ± 0.6	<0.01
Ischemia unchanged	10	4.0 ± 3.1	1.3 ± 2.0	<0.05

Note: [a]Paired *t*-test.

who do not, the difference in mean GHQ is more than 50% greater among Improved patients than among those who have Unchanged perfusion (5.17 vs. 2.99). The increase for the improved group is statistically significant at $P<0.01$ while that the unchanged group is below statistical significance at $P<0.07$. The General Symptom Index of the SCL-90-R, an indicator of global severity combining numbers of symptoms and intensity of distress, is significantly reduced for the total sample after EECP (0.14 ± 0.03, $P<0.001$). Sets of patients with improved perfusion (0.13, $P<0.05$) and those with unchanged perfusion (0.15, $P<0.05$) experience a significant reduction in mean level of general symptoms as measured on this index after EECP. The SCL Positive Symptom total, number of symptoms endorsed, shows amelioration with EECP that is statistically significant for the total sample (5.57 ± 1.62, $P<0.001$) and for the subset of patients with improved perfusion (5.68 ± 1.81, $P<0.01$). Patients with unchanged ischemia have almost the same magnitude of decrease in positive symptoms, but the change is not statistically significant because of a large standard deviation. On the other hand, the SCL-90-R Positive Symptoms of Distress Index, a measure of pure symptom intensity, does not improve for the total sample of patients treated with EECP; however, the subset of patients with improved myocardial perfusion does show significant amelioration (0.15 ± 0.07, $P<0.05$).

EECP treatment is strongly associated with lower levels of depression. Mean BDI after a course of EECP is significantly lower for the total sample (3.50 ± 0.82 , $P<0.001$), a decrease experienced both among patients with improved perfusion (3.11 ± 0.97, $P<0.01$) and unchanged perfusion (4.10 ± 1.47, $P<0.05$). The SCL-90-R Depression Symptom subscale is significantly lower for the total sample (0.18 ± 0.05, $P<0.01$) and this decrease is significant among patients with Improved perfusion (0.19 ± 0.05, $P<0.01$) but not patients with Unchanged perfusion (0.15 ± 0.09, $P<0.13$).

After EECP treatment, some indices of anxiety are significantly reduced. The STAI-Anxiety State is ameliorated significantly for the total sample (1.95 ± 0.83, $P<0.05$), but the amelioration is significant only for patients who have unchanged myocardial ischemia on thallium scan after EECP (4.63 ± 1.53, $P<0.05$). After EECP, reduction in STAI Anxiety Trait is not statistically significant for the total sample; however, the subset of patients with unchanged ischemia do experience a significant amelioration in anxiety trait (1.88 ± 0.69, $P<0.05$). The SCL-90-R Anxiety subscale symptoms did not change significantly with EECP.

Measures of anger and hostility, including the STAI Anger State and Anger Trait and the SCL-90-R Hostility subscale, show small changes after EECP but lack a clear

TABLE 2. Differences in means on psychosocial tests taken before and after enhanced external counterpulsation (EECP)

	Difference of Means		
	Total Sample	**Ischemia Improved**	**Ischemia Unchanged**
General Measures			
GHQ	4.33 ± 1.13^{c}	5.17 ± 1.60^{b}	2.99 ± 1.45
SCL—General Symptom Index	0.14 ± 0.03^{c}	0.13 ± 0.04^{a}	0.15 ± 0.06^{a}
SCL—Positive Symptom Total	5.57 ± 1.62^{b}	5.68 ± 1.81^{b}	5.42 ± 3.04
SCL—Positive Symptoms of Distress Index	0.10 ± 0.07	0.15 ± 0.07^{a}	0.02 ± 0.15
Depression Measures			
BDI	3.50 ± 0.82^{c}	3.11 ± 0.97^{b}	4.10 ± 1.47^{a}
SCL—Depression	0.18 ± 0.05^{b}	0.19 ± 0.05^{b}	0.15 ± 0.09
Anxiety Measures			
STAI—State	1.95 ± 0.83^{a}	0.43 ± 0.72	4.63 ± 1.53^{a}
STAI—Trait	0.50 ± 0.66	-0.29 ± 0.90	1.88 ± 0.69^{a}
SCL—Anxiety	0.08 ± 0.05	0.04 ± 0.07	0.12 ± 0.08
Anger/Hostility Measures			
STAI—Anger State	0.95 ± 0.65	0.57 ± 0.45	1.63 ± 1.66
STAI—Anger Trait	-0.05 ± 0.74	-1.21 ± 0.87	2.00 ± 1.05
SCL—Hostility	-0.07 ± 0.05	-0.11 ± 0.07	-0.02 ± 0.06
Somatization Measure			
SCL—Somatization	0.29 ± 0.09^{b}	0.35 ± 0.15^{a}	0.19 ± 0.08^{a}

Note: Paired *t*-test:
[a]$P<0.05$
[b]$P<0.01$
[c]$P<0.001$

pattern of response. None of the changes are statistically significant.

The SCL Somatization subscale shows a significant decrease in somatization symptoms for the total sample (0.29 ± 0.09, $P<0.01$) after EECP, a pattern which remained significant both for patients with improved ischemia (0.35 ± 0.15, $P<0.05$) and for those with unchanged ischemia (0.19 ± 0.08, $P<0.05$).

In Table 3, patient level of depression on the BDI parameter was analyzed in more detail. Mean level of BDI for the total sample was 8.88, dropping to 5.40 after EECP; patients with resolved ischemia had a mean level BDI slightly less, 8.40 dropping to 5.33, while patients with unchanged ischemia after EECP had a mean BDI slightly higher before EECP, 9.60, dropping to 5.50 after EECP.

BDI≥10, representing mild to moderate symptoms of depression, was a predictor of increased mortality in post-MI cardiac patients in a study by Frasure-Smith.[1] Overall, 31.6% of the patients in Frasure-Smith's study had BDI≥10; in the present study, 26.9% of patients had BDI≥10 prior to EECP. Baseline, pre EECP, dichotomized BDI differs dramatically between the patients whose ischemia improves with EECP and patients whose ischemia remains unchanged. Pre EECP, 17.6% of Improved patients and 40% of Unchanged patients have BDI≥10. After EECP, only 14.8% of the total sample have BDI of greater than or equal to 10. Among patients who have an improved pattern of ischemia, the percent of patients with BDI≥10 remains exactly the same at 17.6% before and after EECP. In contrast, among patients who have unchanged ischemia, the percent of patients with BDI≥10 drops from 40% prior to EECP to only 10% after EECP. Although it is not evident from the table, in the Improved group of patients, one patient's BDI improved from 14 prior to EECP to 3 after EECP and another patient's BDI increased from 9 prior to EECP to 10 after EECP, leaving the total percent in each subset unaltered.

The results of the QOL Assessment given after EECP are shown in Table 4. A notable finding in this group of patients with refractory angina is that on 11 out of 12 indicators only 1 out of 27 patients reported a worsening of QOL: the same patient recorded worsened status of memory and energy. Looking at the total sample, patients feel that their overall well-being was improved after EECP, with 89% of patients reporting some improvement and over 50% noting noticeable-to-strong improvement in overall well-being. All patients indicated that their ability to work had improved after EECP, of whom 78% indicated noticeable-to-strong improvement. Ninety-three percent of patients rated their energy level as improved after EECP, and 71% indicated a noticeable-to-strong improvement. Health condition of patients had been subjectively assessed to be improved by 96% of patients, with 57% recording a noticeable-to-strong improvement. Other QOL indicators, sleep habits, stress management, family life, social life, sexual activity, memory change, and eating habits, were rated by patients as improved, but more than 50% of patients indicated a slight improvement. Ability to walk is the only indicator in which some patients noted a worse QOL, of some significance in a technology which works by manipulating the legs. Twenty percent developed new difficulty with ability to walk after EECP even though another 55% of patients record that their preexisting difficulty with ability to walk resolved with EECP. 25% note no difficulty with ability to walk either before or after EECP.

Patients with improved perfusion after EECP differ from patients with unchanged perfusion after EECP in their QOL assessment primarily in the percentage reporting Strong Improvement. 18%–29% of Improved patients report Strong Improvement in the top four categories compared with 0%–11% of Unchanged patients. A reciprocal disparity occurs in the Noticeable Improvement category: 18%–47% of the patients with improved perfusion reported Noticeable Improvement in the top four categories compared with 44%–80% of the patients with Unchanged perfusion.

For the fifth question of this study, whether pretreatment

TABLE 3. Change in Beck Depression Inventory (BDI) with enhanced external counterpulsation (EECP) therapy

	Pre EECP				Post EECP		
	Range	Mean ± SD	BDI<10 *n* (%)	BDI≥10 *n* (%)	Range	Mean ± SD	BDI<10 *n* (%)	BDI≥10 *n* (%)
Total sample (*N* = 27)	0–30	8.88 ± 8.18	20(73.1)	7(26.9)	0–23	5.40 ± 6.03	23(85.2)	4(14.8)
Improved (*n* = 17)	0–30	8.40 ± 7.91	14(82.4)	3(17.6)	0–18	5.33 ± 5.72	14(82.4)	3(17.6)
Unchanged (*n* = 10)	1–28	9.60 ± 8.95	6(60.0)	4(40.0)	0–23	5.50 ± 6.80	9(90.0)	1(10.0)

psychosocial testing could identify patients who would respond to EECP with improved ischemia, 40 male patients (age, mean ± SD = 63.79 ± 7.26; range = 46–75) were enrolled according to the criteria detailed above. These patients were given psychosocial testing before EECP only, and indicators of age, SPDA, GHQ, STAI, BDI, and all SCL-90-R indices and subscales were measured. All 40 patients completed the EECP protocol. Of those 40 patients, 26 (65.0%) showed Improved perfusion on stress thallium scan, and 14 (35.0%) had Unchanged perfusion. The perfusion outcome on post-EECP stress thallium imaging was paired with psychosocial variables. Paired *t*-tests were calculated for each psychosocial indicator to determine whether any pre-EECP measure was associated with perfusion outcome. No pretreatment psychosocial variable had a statistically significant association with the posttreatment outcome of improved or unchanged perfusion.

DISCUSSION

To answer the five questions of the study, first, the results of this study support earlier findings that EECP treatment is associated with significant subjective improvement in refractory angina. Patient distress decreased significantly on all measures, both for patients with resolution of ischemia and for patients with unchanged ischemia. The finding that patients with Unchanged ischemia have significantly decreased pain after EECP seems to suggest that their pain had been affected by mechanisms beyond the resolution of ischemia associated with EECP. The finding that their pain measures had been higher prior to EECP than those of patients with Improved ischemia raises the question of whether the unchanged group may have underlying differing characteristics of CAD and ischemia. This will be discussed in more detail below.

Second and third, EECP therapy is associated with significant reduction in patient levels of general psychological distress, depression, anxiety, and somatization. Amelioration in general measures of distress tended to parallel physiologic improvement in ischemia, with only one measure, SCL-90-R General Symptom Index, showing significant amelioration for those with Unchanged ischemia. Depressive symptomatology as measured on the SCL-90-R Depression subscale significantly decreased for those whose ischemia improved; BDI scores decreased significantly in both subsets of patients—those with Improved as well as Unchanged ischemia. The more detailed analysis of BDI in Table 3 indicated that overall, the number of patients who were equal to or above a cutoff level of 10 decreased nearly in half with EECP. STAI Anxiety State and Trait scores significantly decreased only in patients with Unchanged ischemia, with the implication that lower anxiety level is not linked to the resolution of ischemia. Somatization symptoms decreased significantly in both subsets of patients, those with improved as well as unchanged ischemia. Measures of anger and hostility symptoms showed no response associated with EECP therapy, either for patients with improved or unchanged ischemia. These measures of stress do not appear to be linked to EECP.

Fourth, EECP treatment appears to be well-tolerated psychologically and socially. Over 87% of patients noted some improvement in overall well-being, health condition, energy level, and ability to work, whether their ischemia improved or not. The degree of improvement strongly paralleled resolution of ischemia.

Fifth, pretest psychosocial variables had no significant association with the degree to which reversible ischemia is resolved by EECP therapy.

To better understand how EECP may be associated with psychosocial effects in the angina patient, it is useful

TABLE 4. Quality-of-life assessment for total sample, *N* = 27

	Ischemia Improved/Ischemia Unchanged				
	Worse	**Unchanged**	**Slight Improvement**	**Noticeable Improvement**	**Strong Improvement**
Overall well-being	0%	11%(12/10)	37%(41/30)	30%(18/50)	22%(29/10)
Ability to work	0%	0%	22%(24/20)	59%(47/80)	19%(29/0)
Energy level	4%(6/0)	7%(0/10)	22%(24/20)	52%(41/70)	19%(29/0)
Health condition	0%	4%(0/11)	39%(41/33)	42%(41/44)	15%(18/11)
Stress management	0%	58%(44/80)	19%(19/20)	15%(25/0)	8%(13/0)
Family life	0%	59%(65/50)	22%(18/30)	15%(12/20)	4%(6/0)
Social life	0%	63%(65/60)	15%(12/20)	15%(18/10)	7%(6/10)
Sexual activity	0%	78%(77/80)	15%(18/10)	7%(6/10)	0%
Memory change	4%(6/0)	78%(77/70)	19%(12/30)	0%	4%(6/0)
Eating habits	0%	85%(82/90)	11%(12/10)	4%(6/0)	0%
Sleep habits	0%	53%(53/56)		47% Improved (47/44)	
Ability to walk	20%	25% Same: no Difficulty		55% Improved to No Difficulty	

to understand the mechanisms in which EECP is believed to affect CAD and what research has found regarding placebo effects of EECP.

Pre- and posttreatment thallium scans and ETT provide objective evidence that EECP[14–25] is associated with resolution of reversible ischemia in many cases. Tissue pathology in animal studies[18–21] suggest collateral revascularization in the coronary arteries as one physiologic mechanism in which EECP leads to lasting subjective and objective improvement. Patients who have had coronary artery bypass graft surgery before EECP are more likely to have improvement of ischemia;[14–16] researchers have suggested that the larger, patent grafts may increase diastolic aortic retrograde flow and enhance revascularization. Peripheral vascular effects may be another physiologic mechanism, as demonstrated by lower double product on ETT.[34] Remarkably, a 7-week course of EECP has been shown to continue to provide significant benefits in decreased mortality for up to 5 years after treatment.[18,19] With these demonstrated physiologic effects, a question for future study is whether EECP may have other physiologic effects with potential for altering mood and psychosocial state; such as effects on the immune system or heart rate variability or by increased perfusion to the brain and other end organs.

EECP may provide a powerful placebo effect, and angina pectoris is an illness known to have a high placebo response. Benson and McCallis[35] reviewed 1,187 cases and found that five inactive remedies provided an 82.4% improvement rate, which was maintained for over a year. Zheng-Shen-sheng et al.[25] ran a trial using first placebo and then true EECP on each patient, with multiple submaximal exercise tolerance tests (SETTs) as measures of physiological effectiveness, to try to determine whether true EECP was more active than placebo as a treatment. They found that while 10 of 15 cases had varying symptom relief after placebo-EECP courses, no cases had an increase in exercise tolerance on ETT after placebo treatment. With true EECP courses, 14 of 15 cases showed improved exercise tolerance along with angina relief. It is thus clearly demonstrated that EECP has physiologic benefit beyond placebo, but the response of two-thirds of patients reporting symptom relief after placebo EECP is a caution that on our subjective anginal assessments, there may well be a component of placebo effect from this attentive, supportive, caregiving intervention. That the effects go beyond placebo in the present study is demonstrated by improvements in thallium scan in 17 of 27 patients. In future studies of psychosocial effects of EECP, it would be important to have a matched control group with non-EECP intervention for 7 weeks, with pre-and post-EECP psychosocial testing to control for and estimate the effects of placebo.

The amelioration in psychosocial condition and improved quality of life in angina patients after EECP is beneficial. In addition, although it requires further study, it is possible that EECP may lower risk factors in these CAD patients. Negative emotional states of depression and anxiety have been shown to be independent risk factors for mortality and morbidity in cardiac patients.[1–3] One study demonstrated that mental stress-induced ischemia is a significant risk factor for fatal and nonfatal cardiac events independent of age, left ventricular ejection fraction, and history of previous MI.[9] In post-MI cardiac patients, depression increased the risk of MI three to fourfold, even when controlling for the effects of other major coronary risk factors, and with a stronger predictive value for mortality than history of a previous MI.[1–3] The measure of depression which showed the strongest correlation with mortality in a study by Frasure-Smith[1] is the BDI, dichotomized at <10 versus ≥ 10. While negative arousal state confers increased risk, it is not yet established whether reduction of the negative state can reverse the increased risk. Future EECP studies will be designed to test whether EECP, which acts in a novel fashion to affect negative arousal states, has any effect when controlling for other variables on the observed better outcomes in morbidity and mortality in EECP patients.

A variety of physiologic mechanisms have been proposed to link negative arousal states with survival in cardiac patients. Ventricular arrhythmias,[1–3] loss of heart rate variability,[35] lowered ventricular fibrillatory threshold,[8] alterations in myocardial oxygen use with either increased demand or decreased supply,[9] central nervous system induced catecholamine surges,[37] neurotransmitter responses promoting coronary artery vasospasm,[37] endothelial dysfunction,[37–39] altered platelet interactions,[37–39] and altered inflammatory mediators, such as macrophages,[40–41] have all been proposed as physiologic pathology theorized to play a role linking adverse psychological states, such as depression and anxiety and mental-stress induced ischemia to mortality from cardiac events. Depressed or anxious patients do not necessarily have higher rates of the physiologic pathology, but it, in conjunction with negative emotional arousal, can confer risk.[1] Future EECP studies will be designed to include assessment of these physiologic mechanisms that may be affected by EECP.

LIMITATIONS OF THE STUDY

The conclusions that we can draw from this study are limited by the small sample size and inclusion of male patients

only. A selection bias in patients is probable, given that patients had to be able to attend daily treatment for up to 7 weeks; thus it is likely that patients were of higher socioeconomic status (SES), with better access to health care, transportation, and social supports. We did not record for race and SES. Neither placebo treatment nor a control group was studied for comparison, making it difficult to assess the strength of the placebo effect. Long-term follow-up to see if psychosocial effects observed in the study are lasting ones has not yet been done.

Statistical analysis was limited to *t*-tests and differences of means, which is appropriate for this study without a control group, but it limited the conclusions that we can draw from the data. Correlations with morbidity and mortality outcomes were not measured. Parameters used in this study are subjective assessments by patients of their clinical state. Correlation with clinical assessment by DSM-IV criteria for states of depression, anxiety, or other psychopathology are limited to the validity of the indicator in this group of medically ill patients. Although all psychological indicators have been tested on large populations and are reliable and specific indicators of symptomatology, we assume the confirmation that those relationships pertain to this sample of patients, and we did not test this assumption. The degree to which statistical significance in difference of means corresponds to clinical improvement was not verified.

Directionality of cause and effect cannot be determined on the basis of this study, and improvements in physiologic state and psychological/psychosocial state may interact, with each having an effect on the other. Future research will include a larger sample size and control group, with a more diverse set of angina patients, and follow the patients long-term to correlate the psychosocial ameliorations to physiologic improvements and cardiac-related morbidity and mortality. Multiple regression analysis could then examine whether the psychosocial effects of EECP are independent of its physiologic effects and whether they are linked to morbidity and mortality for refractory angina patients.

SUMMARY

EECP does appear to be a well-tolerated treatment modality in terms of psychosocial adjustment. Although it is not conclusive whether EECP is an effective long-term treatment strategy for patients with ischemic heart disease, we state that for short-term psychological and social tolerability it is an excellent strategy. Significant reduction in subjective assessment of pain and disability is experienced by patients with EECP, whether their ischemic heart disease improves or remains unchanged. QOL indices of overall well-being, ability to work, energy level, and health condition are perceived as improved by over 85% of subjects, whether their ischemia improves or remains unchanged. Measures of general health quality (GHQ) and SCL symptom indices are significantly ameliorated, whether their ischemia improves or remains unchanged. If future research can support these preliminary test results with clinically significant data, then EECP will benefit patients by reducing psychological distress and improving QOL.

Among the significant psychosocial effects of EECP measured in this study, the effects on depression and anxiety are of particular importance given that when in a state of negative arousal, these states have been shown to be independent risk factors for mortality in other cardiac patients. Although it is not yet known if amelioration of the negative arousal state can reverse that increased risk of mortality, an intervention such as EECP, if it proves to longitudinally ameliorate both arousal states, might offer the possibility of affecting negative arousal states and lower their effect on mortality. These EECP-induced improvements in mood and stress level may have salutary effects physiologically at the level of the coronary arteries. One might hypothesize that there are changes, perhaps in levels of neurotransmitters such as acetylcholine and serotonin, that may lead to improvement in mood and reduction in stress, which contribute to improved coronary artery function.[37–39] Alternatively or additionally, there may be a neuroimmunologic effect taking place, given the fact that there are now hypotheses involving the macrophage both in coronary artery disease and in depression.[40–41]

We expect that future EECP studies will test these hypotheses. Our future research will continue to look into the questions that we havre raised in our present study.

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