Effects of Enhanced External Counterpulsation on Health-Related Quality of Life Continue 12 Months After Treatment: A Substudy of the Multicenter Study of Enhanced External Counterpulsation

Rohit R. Arora, Tony M. Chou, Diwakar Jain, Bruce Fleishman, Lawrence Crawford, Thomas McKiernan, Richard Nesto, Carol Estwing Ferrans, Susan Keller

ABSTRACT

Background: **The Multicenter Study of Enhanced External Counterpulsation (MUST-EECP) was the first prospective, randomized, blinded, sham-controlled study of enhanced external counterpulsation (EECP) in the treatment of chronic stable angina. We previously reported that EECP therapy lengthens the time to exercise-induced myocardial ischemia and reduces angina. We now describe the effects of EECP therapy versus a sham-treated control group in terms of patients' functioning, their senses of well-being and other Health-Related Quality Of Life (HQOL) parameters from baseline to end of treatment and from baseline to 12 months after treatment.**

Objective: **To determine whether a 35-hour course of EECP affects the HQOL of patients with symptomatic coronary artery disease, 12 months following treatment.**

Methods: **Seventy-one of the 139 patients enrolled in MUST-EECP provided evaluable patient-completed questionnaires at baseline, at the end of treatment, and 12 months post-treatment. The Medical Outcomes Study 36-Item Short-Form Health Survey and the Quality of Life Index-Cardiac Version III were used to assess effects on HQOL.**

Results: **Both groups had similar HQOL scores at baseline. At end of treatment and at 12-month follow up, patients who had active-CP reported greater improvement than those who had inactive-CP in all nine quality of life scales, including ability to perform activities of daily living, ability to work, bodily pain, confidence in health, energy, ability to engage in social activities with family and friends, anxiety and depression, and quality of life issues from the effects of angina on health and functioning. Despite small sample sizes, active-CP patients demonstrated significantly greater improvement at 12 months following treatment in bodily pain, social functioning, and quality of life specific to cardiac patients compared with inactive-CP patients.**

Conclusion: **Significant health-related quality of life improvements were measurable up to 12 months after the completion of treatment with EECP. Improvements in this controlled study are consistent with HQOL changes reported in case series and patient registries. Larger studies are warranted. (J Investig Med 2002;50:25–32) Key Words: angina pectoris • health-related quality of life • enhanced external counterpulsation**

INTRODUCTION

The incapacitating effects of angina pectoris on patients' abilities to work, maintain regular social interactions, and participate in usual activities of daily living is well described.[1,2] Broader life effects of health and disease such as these have come to be known as 'health-related quality of life' (HQOL).[3,4] Reliable, validated HQOL measures have been widely used for a number of years in studies evaluating medical conditions other than angina,[5] but, until recently, relatively few controlled studies have been published in which the HQOL changes that are associated with therapeutic interventions for angina have been evaluated quantitatively.[6–8]

From the Columbia-Presbyterian Medical Center (R.A.R.), Columbia University, New York; Moffit-Long Hospital (T.M.C.), University of California San Francisco; Yale University School of Medicine (D.J.), New Haven, Conn; Lahey Clinic Medical Center (R.N.), Burlington, and Harvard Medical School, Boston, Mass; Grant-Riverside Methodist Hospitals (B.F.) Columbus, Ohio; Presbyterian University Hospital (L.C.), University of Pittsburgh Medical Center, Pa; Loyola University Medical Center (T.M.), Maywood, and University of Illinois (C.E.F.), Chicago, Ill; and Research Triangle Institute (S.K.), Research Triangle Park, NC.

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Address correspondence to: Rohit R. Arora, MD, FACC, New Jersey School of Medicine and Dentistry, 185 South Orange Ave, MSB I-536, University Heights, Newark, NJ 07103-2714. E-mail ararorar@umdnj.edu

Enhanced external counterpulsation (EECP) is a non-invasive procedure in which three sets of compressive cuffs are wrapped around the lower extremities. The cuffs are inflated in early diastole and deflated in late diastole to raise diastolic blood pressure and lower systolic pressure. A course of treatment normally involves 35 hours of EECP treatment given for one hour daily.

EECP's effectiveness for angina was established in Multicenter Study of Enhanced External Counterpulsation (MUST-EECP), a randomized, double blind, sham-controlled trial conducted over a 2-year period. MUST-EECP[9] showed that EECP (active-CP) significantly increased time to exercise-induced S-T segment–depression and reduced angina frequency compared with sham counterpulsation (inactive-CP), which confirms the findings of earlier observational studies.[10–12] While MUST-EECP measured the effects of treatment at the end of a 35-hour course, long-term effects have not been determined systematically. In this trial we tested the hypothesis that, compared with patients who had a sham control, patients treated with EECP experience greater improvement in quality of life, as measured by HQOL instruments, at the end of treatment and at 1-year follow up.

METHODS

Objectives

The design of MUST-EECP, including the sham-treatment and blinding method, is described elsewhere.[9] Standard clinical measures of efficacy were used to ascertain any differences between EECP treatment and the sham treatment. A sub-study to assess HQOL both during treatment and for 12 months following treatment was conducted parallel to the clinical study.

Subjects

One hundred and thirty-nine patients, randomized between May 1995 and May 1997, were entered in MUST-EECP, but two patients dropped out before receiving any treatment. In all, 137 received at least one EECP treatment.[9] Of these, in five cases, the unique patient-identifiers that would allow their data to be used in the HQOL substudy were illegible, so 132 of the original 137 could potentially have been analyzed for this substudy. Seventy-one patients (54%) completed questions for the primary HQOL parameters at baseline, end of treatment (EOT), and 1-year follow up. The 71 patients with complete data we refer to as 'evaluable patients.'

Eligibility required patients to (i) be between 21 and 81 years of age, (ii) have symptoms consistent with Canadian Cardiovascular Society Classification angina levels I, II or III, (iii) have documented evidence of coronary artery disease (CAD), and (iv) have an exercise treadmill test (ETT) that is positive for ischemia. Patients were excluded if they had medical conditions that would contraindicate EECP or interfere with trial measures, or who were enrolled in other trials.

Patients enrolled in MUST-EECP were asked if they would complete HQOL questionnaires during the course of treatment. The period of follow up was treatment time plus 12 months. Institutional review boards at each of the study centers approved the MUST-EECP study protocol, inclusive of the HQOL study protocol, and the study was conducted in keeping with the Declaration of Helsinki. All patients gave written informed consent.

Procedure

Before randomization, medical histories were taken and patients were given physical examinations. At baseline and at EOT, ETT was performed and data on frequency of anginal episodes, nitroglycerine (NTG) usage, and on HQOL were collected. At 1-year follow up only, HQOL data were collected. Details of the measurement of ETT, anginal episodes, NTG usage, and adverse events are published elsewhere.[9]

All medications (except on-demand NTG) remained unchanged from baseline to EOT. Once randomized, patients were scheduled for 35 hours of either active-CP or inactive-CP applied in 1-hour intervals, once or twice per day. EOT was defined as 34 or more treatment sessions.

Study patients completed baseline questionnaires before their first treatment sessions. Immediately after the treatment period, compliant patients completed the questionnaires on-site. Study coordinators at each study center distributed and collected materials. Patients completed questionnaires independently with no assistance from a site coordinator or EECP technician. A few patients who had difficulties with the English or Spanish of the questionnaires obtained help from interpreters. Coordinators reviewed each questionnaire for completeness but did not discuss the responses with study subjects. At EOT, patients were given follow-up questionnaires to complete at their convenience and return by mail. Follow-up questionnaires were mailed 12 months after completion of treatment, but unblinding took place 12 months after the last patient had completed treatment. Despite assiduous telephone follow up by site coordinators, fewer patients than had been expected were willing to complete and return questionnaires. The 54% who did return evaluable information was a larger proportion, however, than has been noted in some studies of angina patients.[13]

HQOL Parameters

We followed the recommended procedures for the assessment of our HQOL data, which calls for the inclusion of measures of generic (applicable across conditions and samples) and condition-specific (appropriate to a particular health condition) HQOL.[14,15] The generic measure allows comparisons of HQOL burden across different conditions and treatments, and the specific measure may have more face validity for patients and be more sensitive to treatment effects. Accordingly, we chose the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) as our generic instrument and the cardiac version of the Quality of Life Index (QLI) as the condition-specific measure.

The SF-36 is a widely used, brief but comprehensive measure of general health.[16–18] As the name implies, the SF-36 comprises 36 items that yield eight multi-item scales that measure physical functioning, work role disability due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, work role disability due to emotional problems, mental health, and a single-item evaluation of change in health. Reliability and validity of the SF-36 across diverse populations and health conditions is well documented.[19–22] General population norms exist to interpret scale scores for both the self-administered and telephone-administered versions.[23]

The QLI focuses on a respondent's satisfaction with the areas of life important to him/her. The questionnaire is self-administered in two parts: Part 1 measures satisfaction with various aspects of life as they are impacted by the respondent's cardiac health; Part 2 measures the importance of these same aspects of life to the respondent personally. Scores are calculated by weighting the satisfaction responses according to the importance of those responses, so that they reflect the level of satisfaction with those aspects of life that matter most to the individual. Reliability and validity of QLI in cardiac populations are well established.[24–27]

Statistical Analysis

Of the 71 evaluable patients, 36 were in the active-CP group and 35 were in the inactive-CP group. Of 61 patients not evaluable, 31 were active-CP and 30 inactive-CP. We looked at the relationship between evaluable status and treatment-group assignment and found this to be independent ($P = 0.99$).

A small number of evaluable patients had not completed the full 35-hour course of treatment, but no patient had fewer than 5 hours. Where complete data were available for patients at baseline and at 12-month follow up but not at EOT, the patient's last set of complete data before EOT were carried forward.

Based on relevance to angina pectoris and the characteristics of study population, we pre-specified a subset of four of the nine HQOL scales to serve as our primary parameters. Patients who had complete data sets for each of these four scales at each of the three time points constituted the study cohort. The impact of angina on patients' lives is its interference with physical and role functioning through bodily pain or the effort made to avoid it.[28]

Accordingly, we selected the SF-36 scales of Physical Functioning, Bodily Pain, and Social Functioning, and the cardiac version of the QLI scale of Health and Functioning as primary parameters. Both generic health (SF-36) and angina-specific health-related quality of life were, therefore, included in the primary parameters. We also conducted treatment comparisons on the other SF-36 scales and used all available data. The data for these parameters are, however, not strictly comparable one to the other, because the sample sizes varied slightly across the scales.

Two sets of HQOL parameters, defined as the change from baseline to EOT (EOT analysis) and as the change from baseline to 1-year follow up, were applied, and their scales scored according to standard scoring algorithms.[25] Change scores were defined as baseline scores subtracted from either EOT or 1-year follow-up scores. Because each scale has a different expected variability in clinically stable patients, the magnitude of raw-score change cannot be compared across scales. Change across the scales is made comparable by expressing the magnitude of observed change in terms of expected variability in stable patients. Thus, in order to facilitate correct interpretations of the comparisons, HQOL change scores were transformed into standard deviation units (magnitude of change divided by the population standard deviation for the scale).[29–32]

Scores from multi-item HQOL scales are treated as continuous variables in statistical analyses.[33,34] We tested for statistically significant observed changes in HQOL by performing within-group analyses. Two-tailed *t* tests were used to determine the probability that an observed improvement or decline in HQOL was different from zero at conventional levels (change was considered significant if the probability of observing a change that large was ≤ 0.05). To test for a treatment effect on change in HQOL, analysis of covariance was conducted in which change scores were regressed onto treatment-group membership and baseline scores using general linear models, and the significance of the independent effect of treatment was defined at conventional levels ($P \leq 0.05$). Individual differences among patients were dealt with by randomization to treatment, the subtraction of baseline values, and by

using the baseline measure as a covariate in the models. In addition, we evaluated differences in HQOL between treatment and control groups at baseline.

RESULTS

Sample Characteristics

Patient characteristics in the smaller HQOL cohort (71 patients) were similar to those of the study population as a whole. In both cases, compared with the inactive-CP group, the active-CP group had a longer history of angina. In addition, more patients in the active-CP group had histories of myocardial infarction (MI), and more were classified as Canadian Cardiovascular Society Class III at randomization. In all other respects, including HQOL scores at baseline, the two groups were comparable (Table).

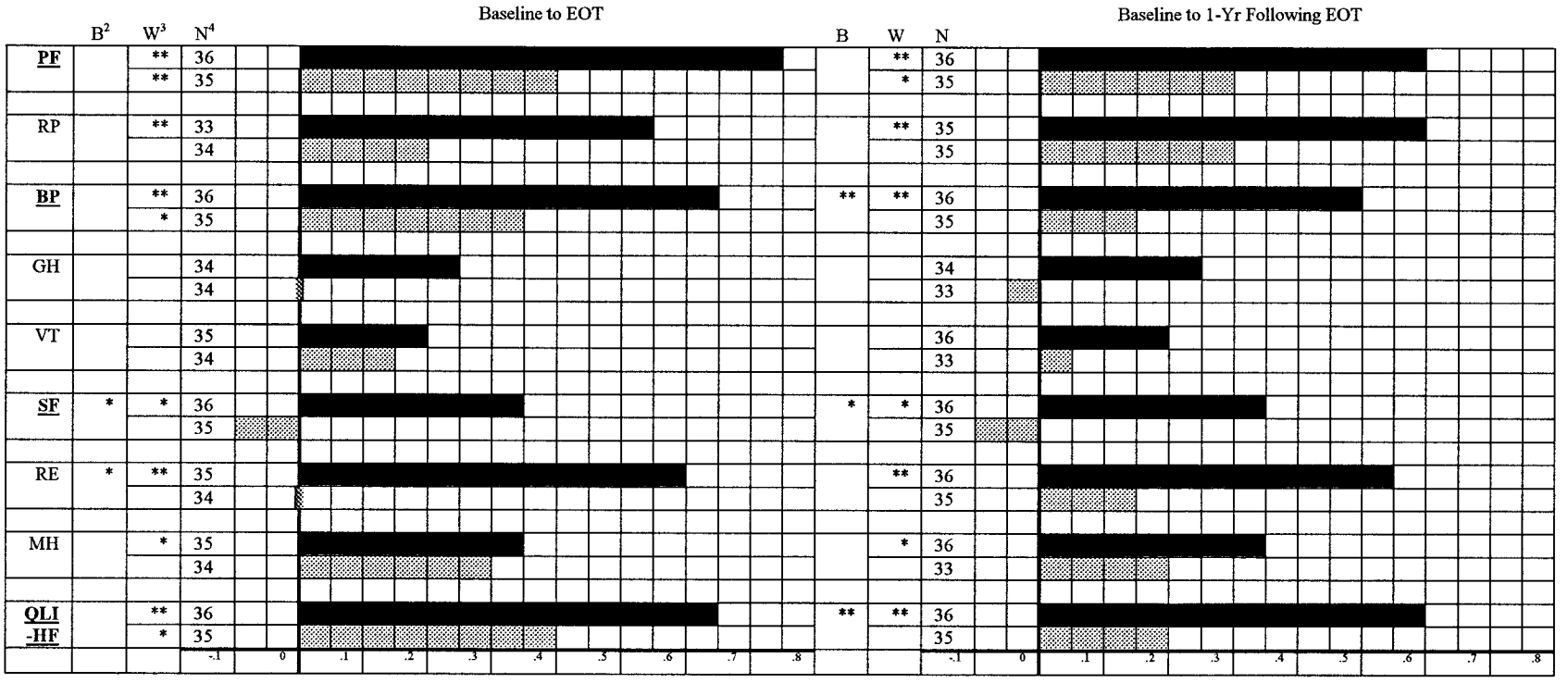
Similarly, the cohort of patients for whom evaluable data were not available was similar to the population as a whole. In order to determine possible differences, we compared baseline characteristics along with pre-treatment and post-treatment ETT data for the cohort of patients in the HQOL substudy with the cohort who lacked questionnaires. In most respects, there were no differences, but in the cohort without evaluable HQOL data there was a trend toward younger patients (averages 54 years vs 65 years), who had suffered MI (38% vs 29%), and who had relatively more angina disability (with 82% being CCS II/III vs 66% for the evaluable group). Although HQOL measures have been reported to be independent of disease severity, results may have been different if all patients had completed questionnaires. There were no meaningful differences between the two cohorts with regard to ETT measures.

Patient characteristics.

	Inactive-CP	Active-CP	*P*
n	35	36	
Age, years, mean±SD	62.7±9.2	65.3±8.1	>0.1
Male, percentage of study population	33, 94.3%	32, 88.9%	>0.4
Race, percentage of study population			>0.6
White	33, 94.3%	31, 88.9%	
Black	1, 2.9%	2, 5.6%	
Asian	1, 2.9%	2, 5.6%	
Cardiovascular history			
CCSC for angina			0.04
I	10, 28.6%	14, 38.9%	
II	14, 40.0%	20, 55.6%	
III	11, 31.4%	2, 5.6%	
Angina, years (mean±SD)	4.48±4.01	9.48±8.46	0.002
Previous MI	10 (28.6%)	19 (52.8%)	<0.05
Previous coronary artery bypass grafting	17 (48.6%)	14 (38.9%)	>0.4
Previous percutaneous transluminal coronary angioplasty	15 (42.9%)	11 (30.6%)	>0.3
Residual vessel disease			>0.3
0	4, 11.4%	1, 2.8%	
1	13, 37.1%	12, 33.3%	
2	7, 20.0%	13, 36.1%	
3	7, 20.0%	7, 19.4%	
No Data	4, 11.4%	3, 8.3%	
Cardiovascular medications			
Nitrates	29, 82.9%	26, 72.2%	>0.3
ASA	31, 88.6%	31, 86.1%	1
CCB	17, 48.6%	23, 63.9%	>0.2
BB	29, 82.9%	23, 63.9%	0.11
Lipid-lowering agents	19, 54.3%	22, 61.1%	>0.6

Extent of Health-Related Quality of Life Changes using SF36 and QLI - HF instruments

Magnitude of Improvement or Decline Expressed in Standard Deviation Units[1]



[1]Observed change in scale scores is divided by the standard deviation for that scale in the general U.S. population rather than the standard deviation of the study data. This permits expression of change in relation to the expected variability for the scores and standardizes comparisons among scales and between the same scales at different time points.
[2]Significance level is associated with the size of the regression weight for treatment group membership indicating whether membership was significantly associated with observed change in scale scores after adjusting for baseline level of HQOL. All data used for these analyses come from the study sample.
[3]Significance level is associated with a t-test that the change that occurred is so large that it is very unlikely to be due to chance. All data used for these analyses come from the study sample.
[4]The sample for the four primary HQOL parameters (PF, BP, SF, HF) was held constant across these parameters and across time. Sample sizes for the other HQOL parameters used all available data. Therefore, only data for the primary HQOL parameters are strictly comparable. Primary parameters are **bold** and underlined.

PF=Physical Functioning
RP=(work) Role disability due to Physical health
BP=Bodily Pain
GH=General Health
VT=Vitality
SF=Social Functioning

Abbreviations
RE=(work) Role disability due to Emotional health
MH=Mental Health
QLI-HF=Cardiac-specific Health & Functioning
B=Between group statistical significance of difference in change
W=Within group statistical significance of change
N=Sample size

Legends
Active CP – Treatment Group
Inactive CP – Sham Group
* Probability of difference this large at <.05
** Probability of difference this large at <.01

Baseline to EOT

Both active-CP and inactive-CP groups reported significant improvements in physical functioning, bodily pain, and cardiac-specific health and functioning from baseline to EOT (third column, left side, Figure). The size of the improvement in HQOL parameters was always larger for the active-CP than for inactive-CP (left side, Figure); however, this difference was only statistically significant for one of the four primary parameters: social functioning (second column, Figure). Those in the active arm reported a substantially greater increase in their abilities to participate in social activities with family and friends than did those in the inactive arm, who, on average, reported a decrease in social activity.

Baseline to 1-Year Follow Up

At 1-year follow up, the active-CP group maintained statistically significant improvements in HQOL across all primary HQOL parameters, whereas the inactive-CP group only maintained a significant improvement in the physical functioning scale, although reduced in magnitude (right side, Figure). The decrease in bodily pain and increase in social functioning held steady for the active-CP group for 12 months following treatment; however, improvement over baseline in physical functioning and cardiac-specific health and functioning was slightly less at 1-year follow up than it had been at EOT. By contrast, inactive-CP lost ground on all scales except social functioning, in which it maintained the decline from baseline observed at EOT. At 1-year follow up, improvements for the active-CP group were significantly greater than those for the inactive-CP group on three of four primary parameters: Bodily Pain, Social Functioning, and Cardiac-Specific Health and Functioning (first column, right side, Figure).

Summary

The HQOL improvement scores of active-CP patients were larger than those of inactive-CP group across nine different measures and over two study periods. These comparisons were more noticeable at 1-year follow up than at EOT. Although the study was underpowered, statistically different between-group treatment effects were nonetheless observed for three of the nine HQOL scales at the EOT and in the follow-up analyses. At the EOT and 12 months following treatment, active-CP patients reported significantly less restriction of activities with family and friends and significantly greater satisfaction with important aspects of their health and functioning than did the inactive-CP group. Twelve months following treatment, EECP patients reported less pain and less interference of pain in daily activities. The HQOL results reported here are concordant with what has been noted in earlier observational studies[35,36] and with the results of the clinical part of this study.

DISCUSSION

HQOL Changes

Compared to inactive-CP, active-CP achieved a number of significant HQOL improvements through 12 months post treatment. These included significant reductions in extent and interference of pain and significant reductions in limitations in activities with family and friends.

In the baseline-to-EOT period there was a tendency for patients in both groups to report improvement in HQOL parameters. These findings suggest that patients in the inactive-CP group may have experienced placebo benefit from the daily attention received throughout the treatment period.[37] The magnitude of the improvement trend was wholly greater with active-CP than with inactive-CP, and in the case of the inactive-CP group, when the daily visits ceased at the end of the treatment period, the improvements in HQOL diminished conspicuously.

Although it remains to be demonstrated, it is believed that protracted cycles of hemodynamic shifts during EECP treatment, which are similar to those seen during vigorous exercise,[38] may stimulate endothelium-mediated intramyocardial vessel growth or restoration of flow reserve, or both.[39,40]

If this is the case, the "healing" effects of this treatment might have continued in the post-treatment phase, and that may account for the widening of the difference between the active-CP and inactive-CP groups during the follow-up period. Another explanation may be found in a possible post-treatment behavior differences between the two groups. If for example, the active-CP group were enabled, and did in fact engage in more exercise, this might also account for some of the difference. Unfortunately, during the 1-year post-treatment period, the recording of any changes or events in patients' statuses was so uneven as to render the data unanalyzable.

Study Limitations

Typically, HQOL parameters require 100–150 patients per arm (200–300 total) in order to detect moderate treatment effects.[30–35] Because the HQOL portion of the MUST-EECP was an adjunct to the main study, sample size was determined by the power requirements for main study parameters rather than for HQOL parameters. For this reason and because of low patient response, only about 25% of the prescribed sample size became available for analysis. It was, therefore, only possible to detect very large HQOL-effect sizes, which

were in fact seen for some HQOL parameters. Nevertheless, to ascertain more completely the HQOL effects of EECP, future research must be of a much larger population sample.

While the active-CP and inactive-CP patients were comparable at baseline, our results may have been different from those reported if all patients had completed questionnaires. We compared baseline characteristics along with pre-treatment and post-treatment ETT data for the cohort of patients in the HQOL substudy with the cohort who lacked questionnaires in order to determine possible differences. In most respects, there were no differences, but in the cohort without evaluate-able HQOL data there was a trend toward younger patients (averages 54 years vs 65 years), who had suffered MI (38% vs. 29%), and who had relatively more angina disability (with 82% being CCS II/III vs 66% for the evaluate-able group). There were no meaningful differences between the two cohorts with regard to ETT measures.

We analyzed the HQOL substudy separately from the main study, and we do not know whether our HQOL results correlate with those of the ETT and symptoms at EOT. Furthermore, counts of angina episodes were not collected at 1-year follow up. We cannot, therefore, determine whether the sustained improvements in HQOL reported here would be evidenced in more traditional measures of clinical effect 12 months after treatment.

CONCLUSIONS

In this small controlled study, substantial HQOL benefits that persisted for at least 12 months after treatment were seen with active-CP but not with inactive-CP patients. This interesting observation may have been a result of patients capitalizing on improved exercise capacity after treatment, or of salutary cardiovascular effects that were triggered during treatment and extended to 1-year follow up. Studies in an appropriately sized study population are warranted and desirable to confirm these noteworthy findings.

APPENDIX

MUST-EECP Trial Coordinators

Columbia-Presbyterian Medical Center: Christine Constantine, RN; Patricia Blowers, RN; Christopher Kaszubski, RN; and Patricia Pugni, RN. Mofitt-Long Hospital: Kim Prouty, RN; Olga Dimitratos, RN; and Xian-Hong Shu, MD. Yale University School of Medicine: Poonamma Chanada, MD; Sanila Rehmatullah, MD; and Neil Jairath. Beth Israel Deaconess Hospital: Carol McKenna, RN; and Peggy McGowan-Gump, RN. Grant/Riverside Methodist Hospitals: Karen Manzo, RN. Presbyterian University Hospital, University of Pittsburgh Medical Center: Virginia Schneider, RN; Louanne Tempich, RCVT; and Ozlem Soran, MD. Loyola University Medical Center: Ellen Galbraith, RN.

MUST-EECP Organization

Core Laboratory. Cardiology Division, University Hospital and Medical Center, State University of New York at Stony Brook: Peter F. Cohn, MD, FACC; William E. Lawson, MD, FACC; and Lynn Burger, RN.

Data and Safety Monitoring Committee. University of Florida College of Medicine at Gainesville, Florida: (Director) Carl J. Pepine, MD, MACC; Ronald G. Marks, PhD; and Eileen Handberg-Thurmond, PhD.

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