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Benefit and Safety of Enhanced External Counterpulsation in Treating Coronary Artery Disease Patients with a History of Congestive Heart Failure

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Key Words
External counterpulsation · Coronary artery disease · Heart failure, congestive

Abstract
Enhanced external counterpulsation (EECP) is used to noninvasively treat refractory angina patients, including those with a history of heart failure. The International EECP Patient Registry was used to examine the benefit and safety of EECP treatment, including a 6-month follow-up, in 1,957 patients, 548 with a history of heart failure. The heart failure cohort was older, with more females, a greater duration of coronary artery disease, more prior infarcts and revascularizations. Significantly fewer heart failure patients completed the course of EECP, and exacerbation of heart failure was more frequent, though overall major adverse cardiac events (MACE, i.e. death, myocardial infarction, revascularization) during treatment were not significantly different. The angina class improved in 68%, with comparable quality of life benefit, in the heart failure cohort. At 6 months, patients with congestive heart failure maintained their reduction in angina but were significantly more likely to have experienced a MACE end point.

Introduction

In current clinical practice, enhanced external counterpulsation (EECP) is typically used to treat patients with angina refractory to conventional medical therapy who are not good candidates for revascularization. These patients often run a high risk because of age, comorbidity, prior revascularization attempts, extensive coronary artery disease (CAD), previous infarcts resulting in left ventricular dysfunction and congestive heart failure (CHF).

EECP has consistently been shown by both objective and subjective measures to be effective in treating angina patients. Treatment with EECP has increased stress exercise time and time to S–T segment depression and improved stress radionuclide perfusion. Similarly, the patient's functional class, quality of life indices and anginal symptoms demonstrate improvement that parallels the more objective findings [1–4]. These benefits have been demonstrated to be sustained by follow-up radionuclide stress testing and quality of life measures for up to 5 years after treatment [5–8].

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EECP, in addition to its acute hemodynamic and circulatory effects, also produces neurohormonal changes which persist after treatment. Of particular note, treatment results in a progressive increase in nitric oxide levels and a decrease in endothelin 1. By affecting the balance of these potent vasodilators and vasoconstrictors in favor of vasodilation, EECP may potentially benefit patients with left ventricular dysfunction independent of its effect on inducible myocardial ischemia. In patients with ischemic cardiomyopathy, improvement in myocardial perfusion might improve both angina and left ventricular function, yielding a double benefit. The published studies have, however, tended to restrict entry of precisely those patients who are now referred for treatment with EECP. Therefore, it is imperative to evaluate the safety and benefit of EECP in patients at higher risk of cardiovascular events.

Based on our understanding of cardiovascular hemodynamics, angina patients with a history of CHF or with left ventricular dysfunction might be less likely to tolerate EECP and more likely to have treatment events such as pulmonary emboli or exacerbation of heart failure. Patients with CHF are at increased risk of pulmonary emboli because of a diminished cardiac output, high venous pressures promoting venous stasis, associated chronic venous insufficiency and decreased activity. Counterpulsation intermittently compresses the venous beds in the lower extremities, increasing venous return and potentially mobilizing deep venous thrombi. The sudden increase in preload could also potentially cause pulmonary congestion, acute right heart failure, or exacerbate ischemia by increasing wall stress and causing hypoxia.

From a safety perspective, the relative balance of systolic afterload reduction and augmented venous return may be of increased importance in patients with compromised left ventricular function. Because of more extensive coronary and vascular disease and significant comorbidity, the CHF patient may also be less likely to benefit from EECP, and the results of therapy may be less durable.

The present study seeks to characterize angina patients with a history of CHF treated with EECP and analyze their response to therapy. Early and 6-month changes in Canadian Cardiovascular Society (CCS) angina class as well as treatment and follow-up of adverse events are presented and contrasted with the cohort of patients without a history of CHF.

Methods

The International EECP Patient Registry (IEPR) housed at the Epidemiology Data Center of the University of Pittsburgh Graduate School of Public Health was initiated in January 1998 to determine the patterns of use, safety and efficacy of EECP. The IEPR sequentially tracks, across a broad spectrum of participating providers (currently 102 participating centers), the demographics, entry characteristics and outcomes of all angina patients treated with EECP. The IEPR-generated database was used to select the cohort of EECP patients with a history of CHF (CHF cohort) and compare their characteristics and response to therapy with the cohort of patients without a history of heart failure.

EECP was typically prescribed for 35 1-hour sessions over a period of 7 weeks. During treatment sessions, the patients were routinely monitored by electrocardiography, pulse oximetry and finger plethysmography; a nurse was in attendance and a supervising physician was immediately available. An initial and subsequent interval history prior to each treatment, at the end of therapy and at 6 months after treatment was obtained. Interval evaluations included: an evaluation of angina functional class by the CCS criteria, angina frequency and nitroglycerin use, changes in medications, quality of life, interim events (including major adverse cardiovascular events, MACE).

Statistical Analysis

The group of patients with a history of CHF versus those without were compared by χ^2 testing for discrete variables and t tests for continuous variables. Significance was defined as $p < 0.05$. Odds ratios of presence versus absence of risk factors were estimated for outcome events using a logistic regression model. Kaplan-Meier life table analysis was performed to evaluate post-EECP MACE occurrence.

Results

Of 1,957 patients in the IEPR with a 6-month follow-up available as January 2001, there were 548 (28%) with a history of congestive heart disease at baseline.

Demographics

The mean age of the cohort of patients with a history of CHF was 67.1 ± 10.9 years; 72% were male. The patients' average duration of clinical CAD was nearly 12 years with 80% having had a prior myocardial infarction (MI), 86% prior revascularization, 64% percutaneous coronary intervention (PCI) and 71% previous coronary artery bypass grafting (CABG). Triple-vessel CAD was present in 59%, two-vessel CAD in 25 and 11% had single-vessel disease. The mean left ventricular ejection fraction (LVEF) was 39.1%; 36% of the patients had a LVEF of <40% (by echocardiography 42%, multiple gated acquisition scanning 7%, left ventricular angiography 43%, other 8%). The prevalence of cardiovascular risk factors was expectedly high, including: 80% with a family history of premature atherosclerotic cardiovascular disease, 51%

Table 1. EECP patient characteristics by CHF status

	Without history of CHF	With history of CHF	p value
Patients in cohort	1,409	548	
Age, years	66.0 ± 10.5	67.1 ± 10.9	<0.05
Male	78.0	72.4	<0.05
Years since CAD diagnosis	9.5 ± 7.9	11.6 ± 8.1	<0.001
Prior MI	58.6	80.2	<0.001
LVEF	50.0 ± 11.4	39.1 ± 13.6	<0.001
Multivessel CAD	75.9	84.4	<0.01
Prior PCI	58.2	63.9	<0.05
Prior CABG	60.7	70.7	<0.001
PCI/CABG candidate	29.7	15.2	<0.001
Family history of CAD	74.3	79.7	<0.01
Diabetes mellitus	36.9	51.0	<0.001
Hypertension	65.6	73.9	<0.01
Hyperlipidemia	75.7	75.6	NS
Noncardiac vascular disease	26.3	35.3	<0.001
Past/present smoking	69.7	73.4	NS

Data are percentages of patients reporting or mean values ± SD. NS = Not significant.

Table 2. Events occurring during the course of EECP therapy by CHF status

	Without history of CHF	With history of CHF	p value
Patients in cohort	1,409	548	
Mean treatment hours	34.7 ± 10.2	33.1 ± 10.8	<0.001
Completed course	86.2	77.9	<0.001
Angina class decreased	75.1	68.3	<0.01
Unstable angina	2.3	3.1	NS
MI	0.6	1.3	NS
Exacerbation of CHF	0.2	5.5	<0.001
CABG	0.2	0.2	NS
PCI	0.7	0.5	NS
Death	0.3	0.7	NS
Skin breakdown	1.1	0.7	NS
Musculoskeletal problems	0.6	1.6	<0.05
MACE	1.7	2.4	NS
Death, MI, CABG, PCI/UA	3.4	5.3	NS

Data are percentages of patients reporting or mean values ± SD. NS = Not significant; UA = unstable angina.

with diabetes mellitus, 74% with hypertension, 76% with hyperlipidemia and 73% with a history of smoking.

Compared to the cohort of patients without a history of CHF, the CHF cohort was significantly older, with a greater proportion of females, a greater duration of CAD and more prior MI and prior revascularization attempts. The CHF cohort had a significantly higher prevalence of traditional cardiovascular risk factors (family history of premature atherosclerotic vascular disease, diabetes mellitus, hypertension, noncardiac vascular disease), with the exceptions of hyperlipidemia and smoking, which were of equal prevalence in both groups (table 1).

Treatment Course

The CHF cohort patients received a mean EECP treatment course of 33.1 h with 78% completing the course as prescribed. This comprised significantly fewer average hours of therapy than in the non-CHF cohort and re-

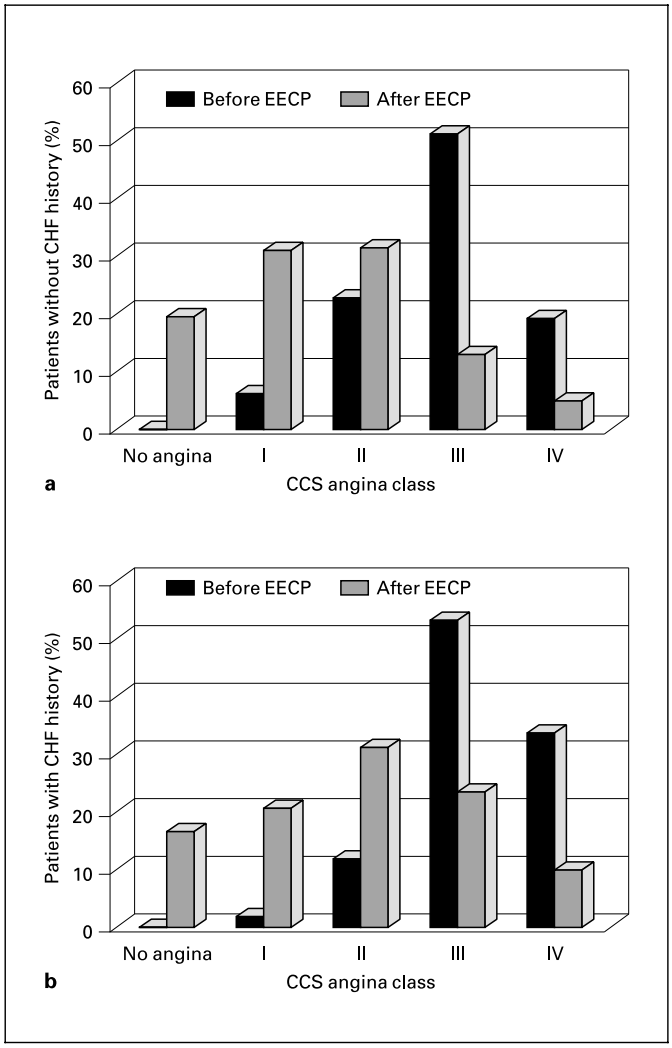

Fig. 1. Effect of EECP on CCS anginal class in cohorts without a history of CHF (**a**, n = 1,409) and with a history of CHF (**b**, n = 548).

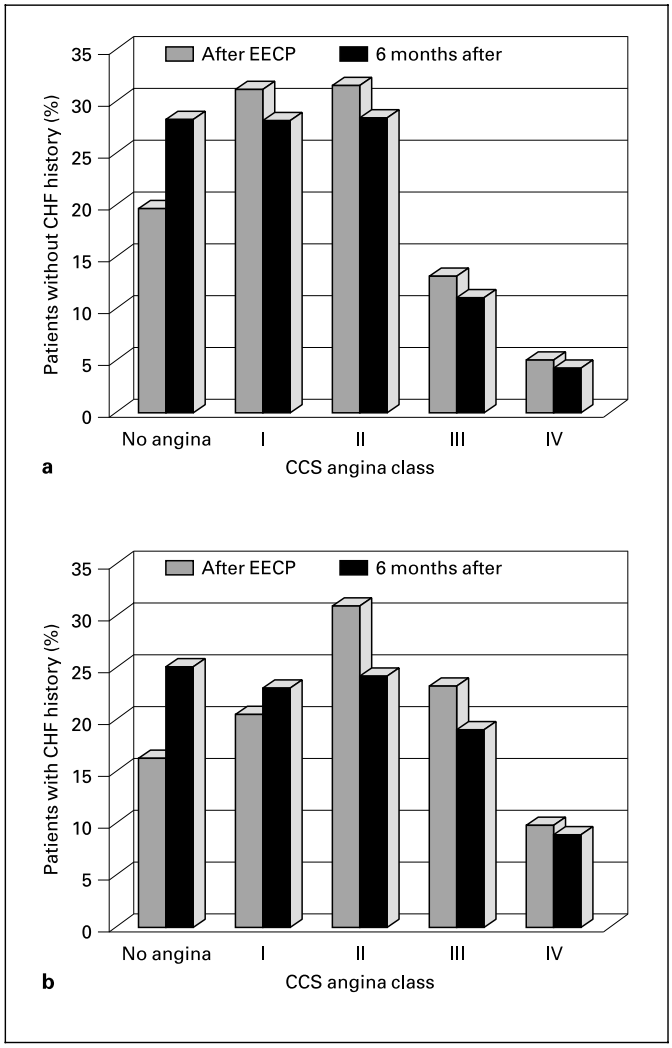

Fig. 2. Six-month follow-up of the effect of EECP on CCS angina class in cohorts without a history of CHF (**a**, n = 1,157) and with a history of CHF (**b**, n = 444).

flected a significantly higher EECP dropout rate. MACE occurring over the course of therapy included: 4 deaths, 7 MI, 1 surgical revascularization and 2 PCI, for an overall MACE rate of 2.4%. This rate is comparable to the rate of 1.7% in patients without CHF. Exacerbation of heart failure was noted in 5.5% of patients with CHF, compared to only 0.2% in those without, a difference which is statistically significant ($p < 0.001$). These events were not attributed to EECP by the investigators. However, the combined end point of death, unstable angina, MI, CABG and PCI (5.3% for the history of CHF group vs. 3.4% for those without) was not significantly increased (p = NS; table 2).

CCS Angina Class

Angina status by the CCS classification is shown in figure 1 for pre- and posttreatment values for the CHF cohort and the group of patients without a history of CHF. Patients in the CHF cohort responded to EECP treatment with angina functional class improving 1 or more classes in 68.0% and worsening in 0.9% of treated patients. Quality of life measures reflected this improvement: 58% of patients assessed their health to have improved; 55% felt the quality of life had improved; 58% felt more satisfied with life. Significant improvement in CCS angina class was demonstrated in both groups. However, in comparison to the cohort without a history of CHF, patients in the

Table 3. Odds ratio for treatment and 6-month benefits and risks in patients with a history of CHF compared to treated patients without a history of CHF

	During EECP treatment		During 6-month follow-up	
	odds ratio	95% confidence interval	odds ratio	95% confidence interval
No reduction in angina	1.40	1.13–1.75	–	–
Exacerbation of CHF	27.08	8.23–89.11	2.01	1.16–3.49
MACE	1.58	0.99–2.54	1.77	1.34–2.39

Table 4. Events occurring during the 6 months following EECP therapy by CHF status

	Without history of CHF	With history of CHF	p value
Patients in cohort	1,157	444	
MACE	8.6	14.4	<0.001
Death	2.2	7.9	<0.001
CABG	2.0	1.1	NS
PCI	2.9	2.5	NS
MI	2.5	3.6	NS
CHF	2.4	7.2	<0.001
Cardiac hospitalization	13.6	19.1	<0.01
Unstable angina	7.4	9.0	NS

Data are percentages of patients reporting. NS = Not significant.

CHF cohort were significantly less likely to have a reduction in their angina with EECP (table 2).

Follow-Up

At 6 months of follow-up, 82% of patients in the CHF cohort without interim MACE reported that their angina was the same or less than immediately after treatment. Overall 75% of these patients had no events and angina the same or improved from after treatment (fig. 2). However, in the 6 months of follow-up, MACE had occurred in 14.4% of patients: death in 7.9%, MI in 3.6%, CABG in 1.1% and percutaneous transluminal coronary angioplasty in 2.5%. Exacerbations of CHF were noted in 7.2% of patients, and 19.1% had been hospitalized for cardiac reasons.

Objective evidence of left ventricular dysfunction served to further stratify the cohort with a history of CHF according to risk. The 176 patients with an LVEF of <35% had a treatment MACE of 2.8% versus 2.1% for the 181 patients with an LVEF ≥ 35%. Exacerbations of CHF during treatment and in the 6-month follow-up were similarly more frequent in those with greater degrees of left ventricular dysfunction. Comparative (LVEF <35% vs. LVEF ≥ 35%) rates of CHF exacerbation were 9.1 versus 4.3% during treatment and 10.9 versus 5.9% during the 6-month follow-up period.

In summary, the mean improvement in CCS functional angina class was less in the CHF versus the non-CHF cohort immediately after EECP, and fewer patients with CHF were able to complete the course of treatment. Stopping treatment for the CHF patients was mainly due to exacerbation of CHF, the rate of MACE during treatment being comparable to that of patients without CHF. In comparison to the patients without a history of CHF, the CHF cohort patients did maintain their angina reduction over the 6-month follow-up period. However, they were significantly more likely to develop exacerbations of CHF and more likely to experience one of the combined end points of MACE – death, MI, CABG, PCI (table 3).

Discussion

Prior pilot reports have demonstrated that angina patients with or without left ventricular dysfunction may be safely treated with EECP. Despite depressed left ventricular function (LVEF < 35%), patients responded to treatment with EECP, demonstrating considerable improve-

ments in angina functional class. While the patients with severe left ventricular dysfunction had a significantly higher mortality rate and more episodes of CHF over the 6 months following treatment, in the majority of these patients the improvement in angina was maintained [9, 10].

In the current study, a history of CHF was a potent predictor of recurrent CHF both during the course of EECP treatment and in the 6-month follow-up period. The CHF cohort of patients included 38.0% with severe left ventricular dysfunction (LVEF <35%). Since EECP increases venous return and preload during treatment, the relative rarity of cases of significant pulmonary congestion suggests that EECP, with appropriate monitoring, may be safely applied in this group of patients.

However, the frequency of exacerbation of CHF during treatment in this high-risk cohort indicates the continued need to take an interim history and to examine the patient prior to treatment for peripheral edema or pulmonary congestion. It also supports the routine use of oximetry and hemodynamic monitoring in patients undergoing counterpulsation and mandates that EECP be performed in an appropriate clinical setting with the immediate availability of highly trained personnel to recognize and treat incipient pulmonary edema.

There were very few reported cases of pulmonary embolism during EECP treatment or in the follow-up in this clinically high-risk population. This suggests that the theoretical concern of precipitating pulmonary embolism by mobilizing lower extremity deep venous thrombi is not a clinically important issue in patients without active thrombophlebitis.

Because EECP increases venous return causing an increase in atrial filling volumes and pressures, atrial arrhythmias and to a lesser extent ventricular arrhythmias were a theoretical concern. However, no clinically important arrhythmias were reported, suggesting that arrhythmias associated with hemodynamic compromise or requiring treatment are a minor concern during EECP.

As may be seen in figures 1 and 2, patients with a history of CHF were likely to enjoy a considerable response to EECP although somewhat less than those patients without a history of CHF. However, both during treatment and in the 6-month follow-up period, patients with a history of CHF had a greater likelihood of cardiac morbidity and mortality (table 4). The likelihood of an adverse cardiac event increased in proportion to the severity of left ventricular dysfunction. Given the severity of the disease suffered by these patients, the treatment and 6-month follow-up MACE are within expectations. More rigorous evaluation of the impact of EECP on these outcomes will require a randomized trial.

Conclusions

EECP is effective in improving angina in coronary patients with a history of CHF. Acute treatment did not cause an excess of MACE in this high-risk group of patients, although 5.5% experienced a worsening of their CHF. At 6 months, in the majority of patients, the improvement in angina demonstrated immediately after EECP is sustained or even slightly improved.

Acknowledgment

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Appendix A

Clinical Sites

Investigators are italicized, coordinators indicated by roman typeface.

New York United Hospital, Port Chester, N.Y.:
J. Tartaglia, MD, D. Fitzgerald, CVT

SUNY Stony Brook, Stony Brook, N.Y.:
W. Lawson, MD, D. D'Ambrosia, RN

Heartcare Clinic of Arkansas PA, Little Rock, Ark.:
C. Fitzgerald, MD, B. Wall, RN

Cardiovascular Research Institute, Columbus, Ohio:
B. Fleishman, MD, K. Manzo, RN

UCSF-Mount Zion, San Francisco, Calif.:
G. Fung, MD, S. Spence, RN

Howard County General EECP Laboratory, Columbia, Md.:
H. Oken, MD, G. Curley, BS, CPT

EECP Center of Northwest Ohio, Toledo, Ohio:
J. Roberts, MD, J. French

Perennia Heart Centers, Norcross, Ga.:
M. Britton, MD, P. Cooke, RN

Southwest Heart, Tuscon, Ariz.:
B. Peart, MD, K. Clark, RN, BSN

Lyford Cay Hospital, Nassau, Bahamas:
C. Tseretopoulos, MD, L. Smith, RN

University of Pittsburgh Medical Center, Pittsburgh, Pa.:
L. Crawford, MD, W. Wade

EECP of Nassau, Valley Stream, N.Y.:
E. Davison, MD, D. Bonagura, RN

Whitaker Wellness Institute, Newport Beach, Calif.:
A. Sosin, MD, A. Johnson, LVN

The Heart-Lung Center, Hawthorne, N.J.:
J. Strobeck, MD, R. Reade, RN

Cardiology and Medicine Associates, Vero Beach, Fla.:
N. Cho, MD, J. Giordano, LPN

Miami Heart Institute, Miami Beach, Fla.:
K. Coy, MD, D. Tabares, RCVT
EECP Center of Northern Virginia, Reston, Va.:
K. Brooks, MD, E. LaRose, RN
Fundacion Clinica Shaio, Bogota, Columbia:
D. Isaza-Restrepo, MD, S. Reyes
Nebraska Heart Institute, Lincoln, Nebr.:
S. Krueger, MD, P. VerMaas, RN, MSN
Brookville Hospital, Brookville, Pa.:
J. Patel, MD, D. Smith, RN
EECP Center of Nevada, Las Vegas, Nev.:
M. McMahon, DO, K. Sponseller, CVT
UPMC-Century Cardiac Care, White Oak, Pa.:
D. Jovanovich, MD, J. Scheponik, RN, CCRN
UCSD Medical Center, San Diego, Calif.:
O. Ben-Yehuda, MD, L. Stocks, RN
HeartGen–South, Indianapolis, Ind.:
S. Adkins, MD, S. Toombs, CMA
Adventist Healthcare Cardiopulmonary, Rockville, Md.:
D. Friedman, MD, G. Driskill, RN
The Cardiovascular Specialists LLC, Falmouth, Mass.:
B. Levy, MD, L. O'Brien, RN, BA
Central Maine Medical Center, Lewiston, Me.:
M. Lanzieri, MD, C. Dominique, RN
Helix Health Centers Inc., Carmel, Ind.:
G. Linnemeier, MD, A. Schwab, RN
Advanced Heart Care, Paris, Tex.:
J. Gladden, MD, D. James
Consultants in Cardiology Inc., Erie, Pa.:
J. Szawaluk, MD, S. Simon, RN
University of Virginia, Charlottesville, Va.:
I. Sarembock, MD, E. Longmoore, CNMT
New York Heart Center, Syracuse, N.Y.:
E. Lozner, MD, K. Lonis, LPN
Central Arkansas Cardiology, N. Little Rock, Ark.:
C. Caldwell, MD, K. Schales, LPN
The Ohio Heart Health Center Inc., Cincinnati, Ohio:
C. Abbottsmith, MD, S. Metze, EMT-P
Mayo Clinic, Rochester, Minn.:
G. Barsness, MD, T. Schnell, RN
Ochsner Foundation Hospital, New Orleans, La.:
M. Mehra, MD, B. Robichaux, RN
Beaumont Hospital, Dublin, Eire:
Prof. *J. Horgan*, D. Dodd, RN
Heart Centers of America LLC, Portland, Oreg.:
R. Schutz, MD, B. Hammock, RN
HeartGen–Midtown, Indianapolis, Ind.:
S. Adkins, MD, S. Toombs, RN
The Heart Center, Huntsville, Ala.:
J. Campbell, MD, J. Owens, LPN
Ocean View Medical Group Inc., Santa Monica, Calif.:
M. Rosenthal, MD, M. Turner
Kaiser Permanente, Denver, Colo.:
D. Flitter, MD, D. Clemetson, RN
Missouri Heart Center, Columbia, Mo.:
R. Doroghazi, MD, J. Quick, RN
Cardiac Disease Specialists PC, Atlanta, Ga.:
H. Sacks, MD, C. Stevenson
Christ Hospital and Medical Center, Oak Lawn, Ill.:
M. Silver, MD, C. Pisano, RN
Central Cardiovascular Associates, Pittsburgh, Pa.:
T. Pinto, MD, L. Tempich, LPN, RC
Chandra Cardiovascular Consultants, Dakota Dunes, S.Dak.:
Y. Moosa, MD, D. Bennett, RN
HeartGen–North, Indianapolis, Ind.:
G. Linnemeier, MD, M. Cox, CMA
Staten Island Heart, Staten Island, N.Y.:
J. Lafferty, MD, L. Ferrara, RN

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