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The Effect of Erythropoietin on Exercise Capacity, Left Ventricular Remodeling, Pressure-Volume Relationships, and Quality of Life in Older Adult Patients with Anemia and Heart Failure with a Preserved Ejection Fraction (HFPEF)

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Abstract

A prospective, open label, 3 month study was conducted to evaluate the feasibility and short term clinical effect of subcutaneous erythropoietin injections in patients with anemia and heart failure preserved ejection fraction (HFPEF; EF=55±2). Using a dose adjusted algorithm to affect a rate of rise in hemoglobin not to exceed 0.4 g/dL per week, hemoglobin (10.8±0.3 to 12.2±0.3 gm/dl) and red blood cell volume (1187±55 to 1333±38 ml) increased with an average weekly dose 3926 units. Functional measures increased from baseline [6 minute walk test (289±24 to 331±22 meters), exercise time (432±62 to 571±51 seconds) and peak VO2 (8.2±0.7 to 9.4±0.9 ml/kg/min)], all $p<0.05$. EDV declined significantly (8% volumetric decrease, 108±3 to 100±3 ml, $p = 0.03$) but there were no significant changes in LV mass or estimated LVEDP. Pressure volume analysis demonstrated a reduction in V30 (e.g. ventricular capacitance) without significant changes in contractile state.

Keywords

Heart Failure; Anemia; Elderly; Ejection Fraction

Introduction

Anemia is a significant co-morbidity among patients with heart failure both in the setting of a reduced and a preserved ejection fraction (HFPEF)(1–3). In subjects with heart failure there is a relationship between anemia, clinical symptoms, left ventricular (LV) structure, hemodynamics, morbidity, and renal function (4–12). Previous studies in patients with systolic heart failure have demonstrated a significant effect of increasing hemoglobin with either erythropoietin (13–18) or iron (17;19;20) on functional capacity, ventricular structure and quality of life, though a recent randomized trial failed to show clinical benefit in such patients(21). Such studies have not specifically focused on the population with HFPEF who account for more than half of the subjects with chronic heart failure.

Chronic anemia is known to result in compensatory left ventricular hypertrophy, higher myocardial chamber volumes, and a high cardiac output state. These structural and

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hemodynamic changes could be detrimental in the population with HFPEF, as the clinical syndrome of heart failure may be exacerbated. Thus, correction of anemia may provide significant benefits in terms of preload reduction, less effort intolerance, less dyspnea, leading to improved quality of life. Accordingly, the primary hypothesis of this prospective open label study is that the administration of subcutaneous erythropoietin to a cohort of anemic subjects with HFPEF would be associated with significant changes in left ventricular structure (reduced end diastolic volume, regressed left ventricular mass) and function (LV chamber contractility, ventricular-vascular coupling, stroke volume and cardiac output) as well as improvements in exercise capacity and quality of life.

Methods

Study design and subjects

This was a prospective, open label, twelve week cohort study among community dwelling, independently living, older adult patients with anemia and heart failure with a preserved ejection fraction. Subjects were recruited from internal medicine clinics, as well as specialty cardiology and renal clinics at an urban medical center setting (New York Presbyterian Hospital, New York City.) The diagnosis of heart failure was based on the NHANES CHF Criteria with a score ≥ 3 (22) and were considered to have a preserved ejection fraction if three-dimensional echocardiographically determined ejection fraction was >45%. Anemia was defined as hemoglobin < 12 g/dL.(23) Informed consent was obtained in all subjects. Columbia University Medical Center IRB approved the study.

Patients were excluded from the study if they had uncontrolled hypertension (SBP >160 mmHg and/or DBP > 90 mmHg, resting heart rate >120 bpm, baseline 6 minute walk > 450 meters, valvular heart disease greater than mild by transthoracic echocardiography, infiltrative cardiac disease such as hemochromatosis and amyloidosis, hypertrophic cardiomyopathy, chronic pulmonary disease (FEV_1 < 60% predicted), renal failure (GFR < 15 mL/min), hemoglobin < 9 g/dL, exercise limited by angina, claudication or neurological diseases, severe liver dysfunction, cardiac surgery less than 3 months prior, known iron deficiency anemia from chronic GI blood loss, uterine bleeding, or other chronic bleeding, significant alcohol or illicit drug use, known hypercoagulable state or an active hematologic disease. Patients were also excluded if they had a history of deep venous thrombosis or pulmonary embolus within 12 months before study entry, had a history of CVA or TIA within 6 months, or an acute coronary syndrome within 6 months of study entry, had an allergy or sensitivity to human serum albumin, or had a known hypersensitivity to mammalian cell-derived products.

Study drug administration and dosing

Epogen (Epoietin alpha), (Ortho Biotec, Inc) was administered weekly by subcutaneous injection using a pre-specified dosing algorithm (See Supplementary Appendix). The dosing algorithm was designed to make adjustments based on the rate of rise (ROR) of the hemoglobin over a one week period, as well as the absolute hemoglobin value. Subjects initially received active treatment with 10,000 units of erythropoietin given weekly by subcutaneous injection. Subjects were carefully monitored (e.g. every week) when beginning therapy to avoid rapid increases in hemoglobin/hematocrit and/or increasing blood pressure control. No dose adjustments were made for the first three doses of erythropoietin (10,000 units/week) unless the hemoglobin rose too rapidly (greater than 0.3 g/dL) in any given weekly interval.

Blood volume analysis

Blood volume was determined after intravenous administration of iodine^{131} –labeled albumin (Volumex, Daxor Corp., New York City, New York) as previously described(24;25). Plasma volume was determined as the zero-time volume of distribution of the radiolabeled albumin obtained by semilogarithmic extrapolation of values measured from at least 3 samples drawn twelve minutes after injection at 6-minute intervals. Spun hematocrit was determined from each sample and plasma radioactivity of each sample was measured in a semiautomated counter (BVA-100 Blood Volume Analyzer, Daxor Corp). Blood volume and red blood cell volumes were calculated from the plasma volume measurement and then compared with normal values for age, gender, height, and weight based on the subject's ideal weight(26).

Two and Three Dimensional Echocardiography

Standard two-dimensional transthoracic echocardiography (2-DE) was performed on each subject. End-diastolic measurements of left ventricular internal dimension (LVID), septal thickness (IVS), and posterior wall thickness (LVPWT) were acquired according to the standards of the American Society of Echocardiography(27). Doppler indices of the mitral inflow pattern including peak E wave velocity, peak A wave velocity and isovolumetric relaxation time (IVRT) as well as lateral mitral annual velocities (e′) were recorded for three beats and averaged. Left ventricular filling pressures were estimated by the formula $EDP=11.96+0.596 \cdot E/e'$ (28).

The equipment and procedures of freehand three-dimensional transthoracic echocardiography (3-DE) have been previously described in detail (29;30). 3-DE was performed using a conventional real-time echocardiograph, three-dimensional acoustic spatial locater, personal computer, and custom software. The data derived includes left ventricular chamber end-diastolic volume (EDV), myocardial volume (MV), stroke volume (SV), and the ejection fraction (EF = SV/EDV). Myocardial volume was multiplied by 1.05 gm/dl to determine ventricular mass. Echocardiograms were performed by study personnel blinded to clinical information.

Functional parameters

Both a six minute walk test (31;32) and cardiopulmonary exercise test were performed at baseline and after 3 months of study drug treatment by study personnel blinded to clinical information. The total distance walked after six minutes to the nearest meter was recorded. Patients performed an upright bicycle exercise test where the workload was increased every three minutes by 25 Watts according to a standard protocol. After 3 minutes of data at rest, exercise began at a workload of 0 W and increased every 3 minutes by 25 W until symptom-limited peak exercise was reached. Expired gas analysis was performed continuously thoughout the test with the Innocor system (Innovision A/S, Odense, Denmark)(33). Expired gas analysis was performed continuously throughout the test with the Innocor system. Peak VO2 was defined as the highest value of VO2 achieved in the final 30 seconds of exercise.

Quality of life

The Kansas City Cardiomyopathy Questionnaire(34) is a valid, reliable, self-administered, 23-item questionnaire that quantifies physical limitations, symptoms, self-efficacy, social interference and quality of life was employed. KCCQ summary score and sub-scores were calculated (range, 0 to 100; higher scores indicate better health status) at baseline at after 3 months of follow-up.

Echocardiographic Estimates of Ventricular Chamber Properties

The ESPVR and EDPVR were estimated using validated single beat techniques. The slope, defining end-systolic elastance (Ees), and a volume axis intercept (Vo) of the end-systolic pressure-volume relationship were estimated non-invasively by the single-beat method (Ees(sb)) described by Chen et al (35). To account for covariancein Ees and Vo both of which determine the position of the ESPVR, the values of these parameters derived from each subject were used to predict the V_{120} (the volume to achieve an ESP of 120 mmHg) which is calculated from the Ees and Vo of each patient: $V_{120} = Vo + 120/Ees$. Effective arterial elastance (Ea), a lumped index of vascular hemodynamic load primarily related to total peripheral resistance and heart rate, was estimated by Ea ≈SV/Pes,(36) where Pes is the LV end-systolic pressure estimated by 0.9 × SBP(37).

To characterize the end-diastolic pressure-volume relationship (EDPVR, where $EDP= \alpha EDV^{\beta}$; α is a scaling constant and β is a diastolic stiffness constant), a recently developed and validated single-beat approach was used(38). This approach relies on the empiric observation that volume-normalize dEDPVRs share a common shape, thereby allowing estimation of and s to define the entire EDPVR from a single measured pressure–volume point. Measured EDP and EDV were used to derive α and β in each subject. To account for covariance in α and β(39), both of which impact on the shape and position of the EDPVR, the values of these parameters derived from each subject were used to predict the EDV at a common EDP of 30 mmHg to yield a pressure-independent index of heart size or ventricular capacitance (EDV_{30}).

The area between the EDPVR and the ESPVR measured as a function of EDP was used to index overall pump function(40;41). This specific area is called the isovolumic pressure-volume area (PVA_{iso}), is independent of after load and can be calculated analytically as a function of LV following curve fitting of the EDPVR and the ESPVR: $PVA_{iso}(V)=\int[P_{es}(V) - P_{ed}(V)]dV = 0.5E_{es}(V-V_o)^2 - V_m(\beta/\alpha)\, e^{\alpha^{*}(V/V)_m}$, where $P_{es}(V)$ and $P_{ed}(V)$ are the end-systolic and end-diastolic pressures, respectively, as a function of volume.

Statistical analyses

Results are expressed as mean ± standard error. Changes in principle measures were compared from baseline to 3 month values by a student's t-test for paired analyses. Associations between changes in hemoglobin and red cell volume measures and outcome variables (LV volumes, functional parameters and quality of life measures) were determined by use of Pearsons' correlation coefficient. The primary endpoint of the study was changes in left ventricular end diastolic volume (LVEDV) after three months of study. Preliminary data indicates that the mean left ventricular end diastolic volume (LVEDV) in patients with HFPEF is 130+/34 ml as assessed by freehand three dimensional echocardiography. With a total of 10 subjects, we had a 90% power to detect a 13 mL (or 10%) difference after 3 months of therapy at an alpha of 0.05. SAS for Windows (Version 8.0, SAS Institute Inc., Cary, North Carolina) was used for all analyses.

Results

Patients enrolled this study were older adult (average age 68 ± 3 years) predominantly female (92%) subjects with several co-morbidities in addition to HFPEF and anemia (See table 1). All of the subjects had a true anemia (defined by the assay as red cell volume <95% predicted(42)) with an average red cell deficit of 503±57 ml (27±8% deficit). Therapy with erythropoietin was associated with an increase in hemoglobin from 10.8±0.3 to 12.2±0.3 g/dl over the course of the study. The rise in hemoglobin was slow and steady (Figure 1) concordant with the dosing algorithm goals and study target hemoglobin of 12.5 to 13.5 g/

dL. The average weekly dose of EPO was 3926 units. Blood volume measurements performed by the I^{131} tagged albumin method confirmed the increase in red cell volume with erythropoietin treatment (from 1187±55 to 1333±48 mL). While the final hemoglobin was below the target hemoglobin range for the protocol of 12.5 to 13.5 g/dL, 6 of 11 individual patients (55%) reached target hemoglobin

No significant changes were noted in systolic blood pressure and a significant decrease was noted in diastolic blood pressure (from 70 ± 3 mmHg to 64 ± 2 mmHg, $p<0.05$) during the study period. This was associated with a modest but not significant change in the number of subjects who were prescribed diuretics and calcium channel blockers but no change in the dose of ACE inhibitors and beta blockers. Plasma volume did not differ significantly from baseline to study termination but trended toward a decrease in volume (from 3066 ± 169 mL to 2942 ± 182, p=ns).

In this cohort of patients, LV end diastolic volume (as measured by 3D echocardiography) decreased with erythropoietin treatment, approximately 8 cc (8%) over the three-month period ($p=0.03$), while LV mass remains unchanged. Pressure Volume relationship of overall cohort pre and post erythropoietin treatment is shown in Figure 2 along with the PVA-iso to EDP relationship. There was a shift in the EDPVR toward smaller volumes, without a significant change in the ESPVR. Overall stroke work, stroke work per grams of ventricular mass and the PVA-Iso area trended toward lower values after 3 months of treatment with EPO.

All measures of functional capacity improved significantly ($p<0.05$) with erythropoietin treatment including peak VO2 (15%), exercise time (32%), and six minute walk duration (15%) (Table 2). Finally, eight of nine scales or subscales on the Kansas City Cardiomyopathy Questionnaire (Table 4) improved, with an average increase of 18 percentage points. However, there were no significant associations between changes in hemoglobin or red cell volume and any functional, structural or quality of life measures.

Discussion

This is the first study to describe the effect of EPO treatment in adult elderly patients with HFPEF and anemia. We explored many potential effects of short term therapy including ventricular remodeling, cardiac output, pressure-volume relationships, and ventricular-vascular coupling, as well as other clinical parameters of functional capacity and quality of life. These data demonstrate that correction of mild-moderate anemia with short term EPO is associated with improvements in functional parameters and reductions in left ventricular volumes and ventricular capacitance without significant effects on systolic properties.

Safety and Tolerability

Widespread enthusiasm for the benefits of erythropoietin therapy was dampened by several studies in patients with chronic kidney disease, trauma and cancer who experienced significant adverse effects from erythropoietin therapy including thrombotic events(43) and cardiovascular events in patients targeted to receive a higher hemoglobin(44;45). Meta-analysis has reaffirmed concerns about an increased risk for death and poor blood pressure control(46) in patients targeted for a higher hemoglobin resulting in the issuance of black box warning by the FDA(47). The FDA recommended careful monitoring of hemoglobin values after dose adjustments, careful monitoring and control of blood pressure along with limiting the rate of rise of hemoglobin to less than 1 g/dl in any 2-week period, all of which were taken into account in the design and execution of this pilot/feasibility trial. The dosing algorithm employed called for weekly monitoring of hemoglobin levels, with dose adjustments that were based on the current hemoglobin level as well as rate of rise in the

preceding week. This algorithm affected a rise in hemoglobin that was slow and steady and did not result in any significant adverse events (e.g. thrombotic episodes or decompensated heart failure or related hospitalization) or any significant increase in blood pressure. Additionally, the dose of EPO employed was lower than anticipated and differed significantly from current treatment guidelines (48). However, such an approach was associated with significant subject burden and alterations in blood pressure medications in a large percentage of subjects (33%). Whether such an approach will be safe and executable in a larger number of subjects is unknown but is being studied currently(49).

Ventricular Structure and Function

The vast majority of patients with HFPEF have concomitant hypertension and a significant percentage have chronic renal dysfunction and left ventricular hypertrophy, all risk factors for the development of HFPEF in large population based studies(50). Anemia contributes to LVH, which is an important underlying substrate among patients with HFPEF. Accordingly, improving anemia in patients with both chronic renal failure and heart failure in meta-analysis has been shown to reduce left ventricular mass and reduce left ventricular volumes. In these studies, average baseline left ventricular mass was significantly higher (289 grams) than in the current cohort and left ventricular end diastolic volume was larger (148 ml). Meta-analysis demonstrated that EPO resulted in significant decline of 15% in LV mass index and 16% in end diastolic volume(51). The discrepancies between these results and ours could be attributable to several factors, including limited sample size of our study, less severe ventricular remodeling in our subjects, short duration (three months compared with greater than 6 months in most trials) of therapy and limited increase in hemoglobin achieved with therapy in the current study. The use of non-invasive pressure volume analysis, demonstrates despite the absence of changes in LV mass; however, there was a trend toward a reduction in ventricular capacitance concordant with ventricular remodeling.

Anemia results in reductions in systemic vascular resistance, increases in sympathetic nervous system activation and expansion of plasma volume which can augment preload volume, contributing to the effort intolerance and dyspnea experienced by subjects with HFPEF. Accordingly, correction of anemia would ameliorate these hemodynamic changes resulting in declines in EDV, stroke volume and cardiac output. Accordingly, treatment of anemia through an amelioration of altered loading conditions would be anticipated to reduce ventricular work, as shown in the reduction in the pressure volume area (Figure 1, bottom panel).

Functional Capacity and Quality of Life

Effects of EPO on quality of life have been limited predominantly to the cancer population, with a Cochrane Review suggesting that therapy may improve Quality of Life and functional class(52) in this population. As well in pre-dialysis patients and dialysis patients, EPO corrects anemia and also improves quality of life and sub-maximal exercise performance(53–55). However, for heart failure subjects limited data are available. Early un-blinded studies and phase II results using EPO in patients with systolic heart failure have found overall significant improvements in exercise capacity and quality of life(56;57). However, more recent randomized trials did not demonstrate a significant benefit on exercise duration, New York Heart Association class, or quality of life score compared with placebo(21). Since a majority of heart failure cases involve subjects with a preserved ejection fraction who have a similar decrement in quality of life as subjects with systolic heart failure(58), characterizing the role of EPO in this population is warranted. While the data from this open label trial are encouraging, with almost all scales and subscales on the KCCQ demonstrating statistically significant increases in scores (concordant with improved

quality of life), compatible with a moderate to large clinical benefit (59), given the un-blinded and open label nature of this study, causality can not be concluded.

Study limitations

This study is limited by its open label design, its limited sample size, and the limited duration of treatment. While the sample size is limited, our study demonstrated the feasibility of performing clinical trials in a patient population previously unstudied and not typically included in clinical trials. Such preliminary data is difficult to obtain for reasons of patient accessibility to study facilities, study subject burden, and patient comorbidities. Our findings can be considered a prerequisite in order to determine relative safety and feasibility of the approach prior to the undertaking of larger randomized phase II-III clinical trials, which are currently underway(49). Notably, in order to safely raise hemoglobin with weekly injections, the study participants were at their target hemoglobin only at the very end of the study period (generally week 11 and 12), and were still anemic for the first two months of the study, which may have blunted the true effect of EPO (or raised hemoglobin) on ventricular remodeling. While we found that the increase in hemoglobin was accompanied by significant increases in functional capacity, improvements in quality of life and reductions in ventricular volumes, these associations cannot be directly attributed to the intervention given the open label study design and absence of statistical correlation and may have occurred by chance or are attributable to some other confounding factor (e.g. medication adjustment).

Conclusions

In a population previously unstudied (older adults with HFPEF and concomitant anemia), erythropoietin was well tolerated and effected a significant increase in hemoglobin and red cell volume without significant increases in blood pressure or other adverse effects during the three month study period. Additionally, there were improvements in exercise capacity, improvements in quality of life and reduced ventricular capacitance during the course of the trial. These data suggest that ongoing evaluation of erythropoietin therapy in subjects with HFPEF and anemia is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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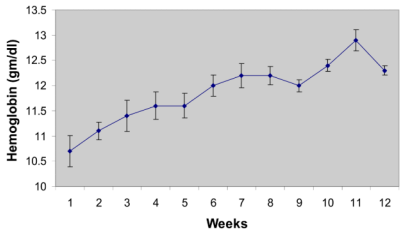

Figure 1.
Hemoglobin Values over Course of Study. Average weekly hemoglobin values are displayed. Values are mean±SE.

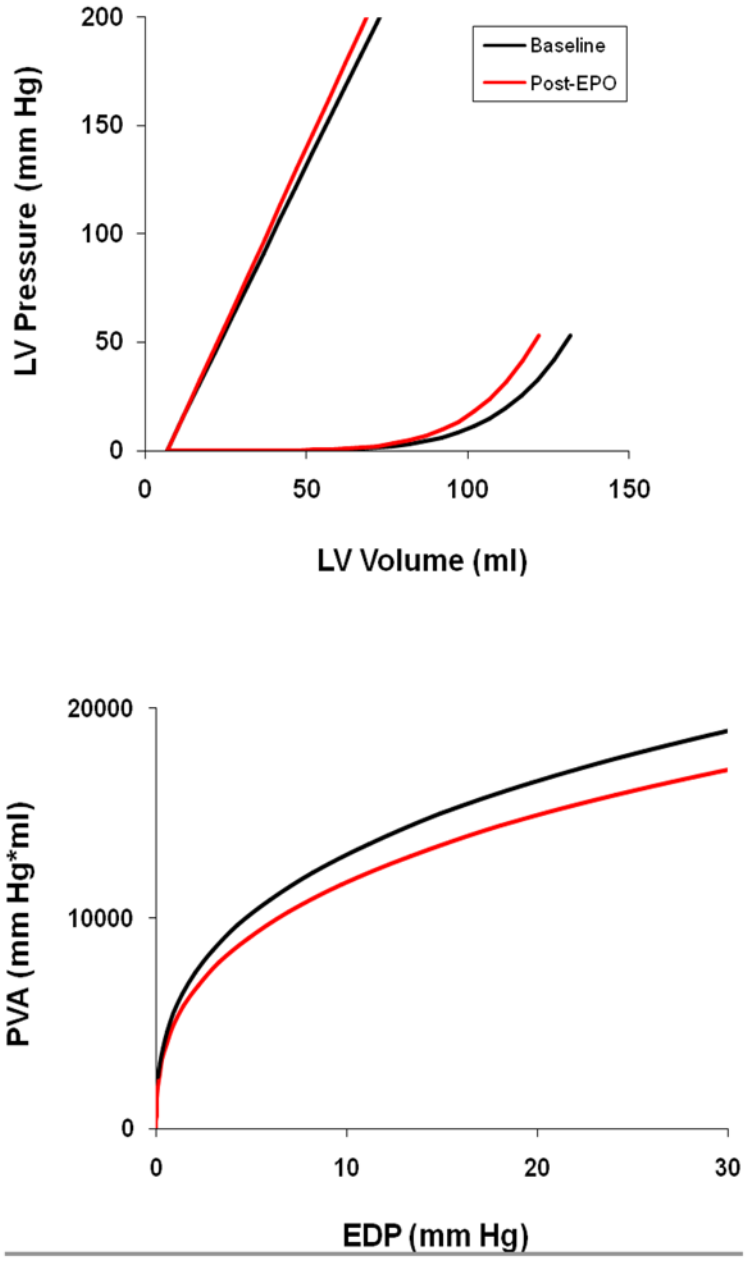

Figure 2.

Group average end systolic and end diastolic pressure volume relations for subjects at baseline (black) and after 3 months of treatment with erythropoietin (red) [upper panel]. The isovolumetric pressure volume area versus estimated EDP at baseline (black) and after 3 months of treatment with erythropoietin (red) [lower panel].

Table 1

Demographic and Clinical Characteristics

Parameter	Result
Number of Subjects	12
Age (years)	68 ± 3 (range 52–86)
Gender (% Female)	92%
Race	8% White
	33% Black (nonwhite)
	58% Hispanic (nonwhite)
Co-Morbid Conditions - n (%)	
Diabetic	8 (75%)
Coronary Artery Disease	8 (75%)
Obesity	10(83%)
Chronic Renal Insufficiency	9 (75%)
Lab Results	
BUN (mg/dl)	35 ± 7
Creatinine (mg/dl)	1.7 ± 0.3
eGFR (ml/min)	55 ± 7
Erythropoietin (mU/ml)	23 ± 4

Table 2

Preliminary Clinical Findings

	Baseline (n=11)†	Follow Up (n=11)
Adverse Events	N/A	0
Hemoglobin (g/dL)	10.8 ± 0.3	12.2 ± 0.3*
Blood Pressure Parameters (mmHg)		
Systolic Blood Pressure	140 ± 6	138 ± 6
Diastolic Blood Pressure	70 ± 3	64 ± 2*
Mean Arterial Pressure	93 ± 3	89 ± 2
Pulse Pressure	71 ± 5	74 ± 7
Medication Use (no. pts (%))		
Diuretic (any type)	8 (73)	10 (91)
Loop Diuretic	5 (56)	6 (67)
Thiazide	3 (33)	2 (22)
ACE Inhibitor	7 (78)	7 (78)
Beta Blocker	6 (67)	6 (67)
Calcium Channel Blocker	6 (67)	7 (78)
Blood Volume Parameters		
Total Blood Volume (mL)	4098 ± 214	4207 ± 223
Plasma Volume (mL)	3066 ± 169	2942 ± 182
Red Cell Volume (mL)	1187 ± 55	1333 ± 48*
Exercise Parameters		
Six Minute Walk Test (m)	289 ± 24	331 ± 22*
Bicycle Ergometer Exercise Time (s)	432 ± 62	571 ± 51*
VO2 (mL/min)	628 ± 51	773 ± 79*
VO2 (mL/kg/min)	8.2 ± 0.7	9.4 ± 0.9*
RER	0.9 ± 0.1	0.9 ± 0.1
Peak Exercise HR (bpm)	96 ± 6	107 ± 6

† Original n=12, one patient discontinued for unrelated medical reasons

* $p<0.05$, Values are Mean±SE

Table 3

Echocardiographc and Physiologic Variables

	Baseline (n=11)	Follow Up (n=11)
2D Echocardiographic Parameters		
Mitral Valve E Velocity	98 ± 7	77 ± 6*
Mitral Valve A Velocity	100 ± 9	93 ± 7
E/A Ratio	1.1 ± 0.1	0.8 ± 0.1*
E′ (Tissue Doppler)	13 ± 0.8	11 ± 1
3D Echocardiographic Parameters		
SV (mL)	59 ± 2	54 ± 2*
EDV (mL)	108 ± 3	100 ± 3*
Ejection Fraction (%)	55 ± 2	54 ± 1
LV Mass (g)	167 ± 7	164 ± 6
Pressure-Volume Parameters		
Estimated LVEDP (mmHg)	16 ± 0.4	16 ± 0.3
Single Beat Ees (mm Hg/ml)	3.0 ± 0.2	3.3 ± 0.2
Single Beat Vo (mL)	7 ± 3	7 ± 2
Pes/ESV (mmHg/mL)	2.6 ± 0.2	2.7 ± 0.1
V120 (ml)	47 ± 3	45 ± 3
V30 (ml)	119 ± 4	111 ± 4†
Stroke Work (mL mmHg)	5441 ± 310	4898 ± 253
Stroke Work/Mass Ratio (mL mmHg/g)	33 ± 2	30 ± 1
PVA-Iso-20 mm Hg (ml * mm Hg)	16239 ± 1035	14876 ± 988

*p<0.05

†p = 0.054. Values are Mean±SE

Table 4

Quality of Life

	Baseline (n=11)	Follow Up (n=11)
Clinical Summary	44 ± 7	64 ± 4*
Quality of Life	38 ± 5	62 ± 3*
Physical Limitations	44 ± 7	65 ± 3*
Functional Status	43 ± 7	63 ± 3*
Symptom		
Frequency	43 ± 8	60 ± 4*
Severity	45 ± 7	61 ± 5*
Change	46 ± 6	53 ± 6
Self Efficacy	46 ± 5	61 ± 4*
Social Interference	52 ± 8	71 ± 5*

* $p<0.01$, Values are Mean ± SE