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Effects of Interleukin-1 Blockade with Anakinra on Aerobic Exercise Capacity in Patients with Heart Failure and Preserved Ejection Fraction (from the D-HART Pilot Study)

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Abstract

Heart failure with preserved ejection fraction (HFpEF) is a clinical syndrome of exercise intolerance due to impaired myocardial relaxation and/or increased stiffness. Patient with HFpEF often show signs of chronic systemic inflammation and experimental studies show that interleukin-1 (IL-1), a key pro-inflammatory cytokine, impairs myocardial relaxation. The aim of the current study was to determine the effects of IL-1 blockade with anakinra on aerobic exercise capacity in patients with HFpEF and plasma C-reactive protein (CRP) >2 mg/l (reflecting increased IL-1 activity). Twelve patients were enrolled in a double-blind, randomized, placebo-controlled, cross-over trial and assigned 1:1 to receive one of the 2 treatments (anakinra 100 mg or placebo) for 14 days and then an additional 14 days of the alternate treatment (placebo or anakinra). Cardiopulmonary exercise testing (CPX) was performed at baseline, after the first 14 days and after the second 14 days. Placebo-corrected interval change in peak oxygen consumption (VO_2) was chosen as primary endpoint. All 12 patients enrolled in the study and receiving treatment completed both phases, and experienced no major adverse events. Anakinra led to a

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statistically significant improvement in peak VO_2 (+1.2 ml•kg^{-1}•min^{-1}, P=0.009), and a significant reduction in plasma CRP levels (−74%, P=0.006). The reduction in CRP levels was correlated with the improvement in peak VO_2 (R=-0.60, P=0.002). Three patients (25%) had mild and self-limiting injection site reactions. In conclusion, IL-1 blockade with anakinra for 14 days significantly quenches the systemic inflammatory response and improves aerobic exercise capacity in patients with HFpEF and elevated plasma CRP levels.

Keywords

heart failure; inflammation; diastole; obesity

INTRODUCTION

Heart failure (HF) is a clinical syndrome of exercise intolerance secondary to impaired cardiac function. Approximately 50% of patients with HF have preserved left ventricular (LV) systolic function (HF with preserved ejection fraction – HFpEF) characterized by impaired LV diastolic filling due to incompletely characterized mechanisms.[1-3] Observational studies have linked markers of systemic inflammation with impaired cardiac function and poor prognosis in patients with HFpEF[4-5] and in patients with chronic inflammatory diseases.[6-8] Interleukin-1 (IL-1) is an apical cytokine involved in local and systemic inflammatory processes.[9] IL-1 induces changes in systolic and diastolic function in experimental animal studies.[10] Patients with rheumatoid arthritis (an IL-1 related disease) show signs of impaired LV diastolic function and treatment with anakinra—an IL-1 blocker—restored normal LV diastolic function within hours of treatment.[7-8] Anakinra is approved for the treatment of chronic systemic inflammatory diseases, and has recently been shown to reduce the incidence of HF following ST-segment elevation AMI and to improve aerobic exercise capacity in patients with HF and reduced ejection fraction (HFrEF).[11-12] We now present the effects of anakinra on aerobic exercise capacity and ventilatory efficiency in a randomized, double-blind, placebo-controlled cross-over pilot trial in patients with HFpEF and systemic inflammation (plasma CRP levels >2 mg/l).

METHODS

The study design was registered in www.clinicaltrials.gov (NCT01542502). An exemption for an investigational new drug use was granted by the Food and Drug Administration. The study was approved by the local Institutional Review Board and all patients provided written consent. Inclusion criteria were age >18 years, New York Heart Association (NYHA) class II-III HF symptoms (without changes in class or treatment in the past 3 months), preserved LV ejection fraction (>50%) with LV end-diastolic volume index (<97 ml/m^2), and evidence of abnormalities in LV relaxation, filling, distensibility or stiffness as defined by the European Heart Society consensus document.[3] Patients were excluded for any of the following conditions: HF hospitalization within the prior 12 months; recent (<3 months) changes in medical therapy for HF; concomitant conditions or treatments affecting completion or interpretation of the cardiopulmonary exercise test (CPX)(i.e. physical inability to walk on a treadmill, significant myocardial ischemia, angina, uncontrolled

arterial hypertension [at rest or during the baseline exercise test], atrial fibrillation, moderate to severe aortic or mitral valve disease, chronic pulmonary disease limiting exertion, or anemia [defined as hemoglobin <10 g/dl]; recent use of systemic immunosuppressive or anti-inflammatory drugs (not including non-steroidal anti-inflammatory drugs); chronic inflammatory or infectious diseases; stage IV-V kidney disease; neutropenia (<2,000/mm^3); pregnancy; any malignancy or any condition limiting survival or ability to complete the study. After initial screening, patients were assessed for systemic inflammation, defined as plasma high-sensitivity C reactive protein (CRP) levels >2 mg/l, using an automated high-sensitivity latex-enhanced assay.[13]

All patients underwent CPX at baseline and upon completion of 14 days and 28 days treatment. The CPX was administered using a metabolic cart that is interfaced with a treadmill (Vmax Encore, Viasys, Yorba Linda, CA). A conservative ramping treadmill protocol was used as described previously.[12] Expired gases were sampled using a mouthpiece-mounted sensor, and analyzed to continuously measure oxygen consumption (VO_2), carbon dioxide production (VCO_2) and minute ventilation (VE). Peak VO_2, the VE/VCO_2 slope, and the oxygen uptake efficiency slope (OUES) were determined as described, with the first measuring aerobic exercise capacity and the other ventilatory efficiency, the ability to expel CO_2 and consume VO_2 at an appropriately low VE.[12,14] All patients also completed a HF symptom questionnaire (Duke Activity Status Index [DASI])[12]. The investigational pharmacist performed randomization using a dedicated randomization algorithm prepared on randomization.com by one of the investigators not involved in the conduct of the study (seed #26404, created on 11/29/2011). For each patient, the pharmacist prepared two indistinguishable sets of 14 syringes containing 100 mg of anakinra (Kineret™, Swedish Orphan Biovitrum, Stockholm, Sweden) in 0.67 mL and matching NaCl 0.9% placebo. Treatment consisted of two courses of 14 daily subcutaneous injections without any washout period. Each patient was randomized to receive either active treatment first followed by placebo, or *vice versa*. All CPXs were performed by a single operator. Data were electronically transferred and all calculations related to the CPX were performed in Dr. Arena's core laboratory. The primary endpoint was the placebo-corrected difference in the interval change in peak VO_2 from baseline to the post-treatment follow-up. Secondary endpoints included placebo-corrected differences in interval changes in CRP plasma levels and ventilatory efficiency (VE/VCO_2 slope and OUES). Sample size calculations relied upon a pilot study of anakinra in patients with HFrEF, in which an identical 14-day treatment with anakinra produced a median improvement in peak VO_2 of +2.8 $ml \cdot kg^{-1} \cdot min^{-1}$, with a standard deviation of 1.2 $ml \cdot kg^{-1} \cdot min^{-1}$.[12] We therefore calculated that a cross-over trial would require a sample size of 14 patients to provide a power of >80% (alpha 0.05) to detect a difference of 1.4 $ml \cdot kg^{-1} \cdot min^{-1}$ with a standard deviation of 1.2 $ml \cdot kg^{-1} \cdot min^{-1}$, and <20% loss to follow up. The values are reported as median and interquartile range to account for potential deviation from the Gaussian distribution. The differences in interval changes between groups are analyzed using a random-effect general linear model for repeated measures analyzing the effects of time and group allocation, comparing on-treatment time 1 and on- treatment time 2, and using baseline time 0 as a covariate,[15] and are presented as changes in the median values for all variables. The Spearman correlation test was used to evaluate correlations between variables.

Statistical significance was set at the 0.05 level and unadjusted p values are reported. Computations were performed with SPSS 21 (IBM, NY, USA).

RESULTS

From January 2012 to May 2013, we screened 23 patients with stable HFpEF (diagnosed according to the ESC criteria)[3] and enrolled 14 with CRP>2.0 mg/l, while excluding the remaining 9 patients with CRP≤2 mg/l (Figure 1): one patient signed informed consent but did not complete any of the study tests nor received treatment, one patient completed the baseline CPX but experienced angina, and therefore was excluded from the study prior to administration of any study treatment. Twelve patients received study medication and were included in the final analysis. Of these, 11 patients (92%) were women, 4 (33%) were self-defined Caucasians and 8 (67%) African-Americans. Median age was 62 years. All 12 patients had systemic arterial hypertension and 3 patients [25%] had echocardiographic evidence of left ventricular hypertrophy. All patients were obese (BMI≥30, median BMI 39 kg/m^2 [range 30-50], with 4 [33%] having BMI>40). Median LVEF was 58% and median E/E' was 11. Six patients (50%) has NYHA class II symptoms and the remaining 6 patients (50%) class III symptoms, with a median duration of symptoms of 20 months (range 6-36). None of the patients had moderate or severe impairment in the glomerular filtration rate (<60 ml/kg/1.73 m^2). All patients were treated with furosemide, 10 patients (83%) were treated with either an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, and 10 (83%) were treated with beta-adrenergic blockers, with all 12 patients (100%) being on either class of drugs and 8 (67%) on both. Two patients (17%) were receiving spironolactone and 11 patients (92%) were treated with a statin plus aspirin. Clinical characteristics of the 12 patients are reported in Table 1.

Six patients received anakinra first and 6 placebo, with the first dose given immediately after baseline CPX. The patients were then given a supply of 13 additional syringes to self-administer at home daily. All 12 patients completed the second CPX 14 days later, received the second batch of (cross-over) syringes, and completed the third CPX an additional 14 days later (see Figure 1). With the exception of the patient who experienced angina during baseline CPX (prior to any treatment), none of the treated patients experienced any serious adverse events or requested discontinuation of treatment. Three patients (25%) experienced mild injection site reactions with anakinra, whereas no injection site reactions were reported with placebo.

On-treatment peak VO_2 was 16.3 $ml \cdot kg^{-1} \cdot min^{-1}$ [13.8-17.5] with anakinra vs. 15.1 $ml \cdot kg^{-1} \cdot min^{-1}$ [11.3-17.3] with placebo, leading to a placebo-corrected difference in median peak VO_2 (primary endpoint) of 1.2 $ml \cdot kg^{-1} \cdot min^{-1}$ (+8%, P=0.009)(Figure 2). Placebo-corrected changes in peak VO_2 for each patient are reported in Table 1. Anakinra treatment also led to a significant reduction in plasma CRP levels (placebo-corrected difference of −6.1 mg/l [-74%], P=0.006, Figure 2). No significant effect was seen on VE/VCO_2 slope, a measure of ventilatory efficiency (Figure 2), however a sensitivity analysis showed a significant improvement in the VE/VCO_2 slope in the subgroup of patients who were above median VE/VCO_2 slope values (>25, N=5) at baseline (placebo-corrected difference 3.8 [12%] favoring anakinra, P=0.047). Treatment with anakinra

improved the OUES, another measure of ventilatory efficiency (placebo-corrected difference 0.14 [7%], P=0.006, Figure 2). The interval changes in CRP levels were inversely correlated with the changes in peak VO_2 (R=-0.60, P=0.002), with greater reduction in CRP being associated with greater increase in peak VO_2 (Figure 3). Similarly, leukocyte count in the peripheral blood was significantly reduced with anakinra (placebo corrected difference −1,300/mm^3, P=0.005, with a 23% reduction in neutrophil count [P=0.007] and a 20% reduction in monocyte count [P=0.039]). Despite small changes in the leukocyte count, it significantly correlated with changes in peak VO_2, with greater reduction (with anakinra) predicting greater increases in peak VO_2 (Figure 4). Conversely, no differences in brain-type natriuretic peptide (BNP) levels changes were observed, nor were the changes correlated with changes in peak VO_2 (Supplemental Figure 1). There was a trend toward greater DASI scores (reflecting improved perceived functional capacity) favoring anakinra (median +5.4 [0/+12.6], P=0.068). Anakinra had no detectable effects on body weight, resting or maximal heart rate, resting or maximal systolic or diastolic blood pressure (data not shown). Although limited by the small numbers, none of the baseline clinical characteristics (such as gender, age, ethnicity, NYHA class, BNP levels, LVEF, E/E' ratio, LVM or left atrial volume, diabetes, medications) explored at sensitivity analyses (using the variable as covariate) influenced the effects of treatment on peak VO_2 (all P values >0.10 for interaction).

DISCUSSION

The pathophysiologic mechanisms leading to exercise intolerance in HFpEF are incompletely understood.[1-3] The results of this pilot study, showing an improvement in aerobic exercise capacity and ventilatory efficiency in patients with HFpEF treated with an IL-1 blocker, suggest that enhanced IL-1 activity may represent an additional mechanism contributing to the pathophysiology of HFpEF. Increased myocardial stiffness and impaired relaxation lead to increased filling pressure and symptoms of pulmonary and systemic congestions in patients with HFpEF. Myocardial stiffness is related to structural changes such as cardiomyocyte hypertrophy and interstitial fibrosis, as well as to molecular changes in the isoform and phosphorylation state of titin, the key protein anchoring the sarcomere to the cytoskeleton providing increased stiffness at the cardiomyocyte level.[2-3] Cardiomyocyte relaxation is, on the other hand, an active process that is modulated by myocardial and systemic factors.[2-3,10,16] None of these factors alone explain the symptoms or hemodynamic changes seen in patients with HFpEF.[2-3] Symptoms, functional limitations, and prognosis in patients with HFpEF are less likely to improve with standard HF treatments which have been shown to be effective in HFrEF, suggesting that the current paradigm of neuro-adrenergic and renin-angiotensin-aldosterone blockade fails to address one ore more key mechanisms involved in HFpEF. Experimental studies in cardiomyocyte cultures and animals show that IL-1 modulates myocardial contraction and relaxation.[10,16] Ikonimidis and coll.[7] described that patients with rheumatoid arthritis, without known cardiovascular disease, had evidence of abnormal myocardial relaxation which improved significantly within 3 hours of a single dose of anakinra, showing that IL-1 activity acutely modulates myocardial relaxation. More recently, the same group confirmed a significant improvement in diastolic function, myocardial strain, and vascular compliance following anakinra treatment also in patients with rheumatoid arthritis and heart disease.[8]

The current D-HART pilot study shows for the first time that patients with stable HFpEF and evidence of systemic inflammation (CRP>2 mg/l) have markedly reduced aerobic exercise capacity, and that treatment with anakinra to block IL-1 activity for 14 days leads to a statistically significant reduction in systemic inflammation and a significant improvement in exercise capacity. The reduction in CRP levels, a surrogate marker for IL-1 activity, correlated with the improvement in peak VO_2. These results confirm the role of IL-1 in regulating cardiovascular function and provide the first evidence that an IL-1-targeted therapeutic strategy may be valuable in HFpEF.

Peak VO_2 was chosen as the primary endpoint for the current study given its long established history as a robust prognostic marker in HF, and is considered the gold standard for quantifying functional capacity.[17,18] The improvement in peak VO_2 seen with anakinra in the D-HART study (placebo corrected difference in median peak VO_2 +1.2 $ml \bullet kg^{-1} \bullet min^{-1}$) appears to be smaller than what has been observed in patients with HF and reduced EF,[12] however there are differences in baseline impairment between HFpEF and HFrEF. Although smaller than expected, the improvement in peak VO_2 is very likely to be clinically relevant, as even smaller improvements were associated with improved outcomes in the HF-ACTION study.[19] The recent RELAX trial had set the very same target on the assumption it would be clinically relevant.[20] Anakinra also improved the OUES and the VE/VCO_2 slope (in those patients with above median values at baseline). Both an elevated VE/VCO_2 slope and diminished OUES reflect ventilatory inefficiency, indicative of increased ventilation-perfusion mismatch, exaggerated mechano- and ergoreceptors, and impaired oxidative capacity of skeletal muscle, and portend a poor prognosis in HF.[21,22]

The choice of 14 days of treatment with anakinra may be viewed as arbitrary. The same regimen has been used in two pilot studies in patients with ST-segment elevation myocardial infarction in which a protective effect against new onset HF was seen,[11,23] and in one pilot study in patients with chronic HFrEF (<40%) in which a significant improvement in peak VO_2 was seen.[12] It is unknown whether changes in peak VO_2 would have occurred even with a single dose or a shorter duration of treatment, or whether anakinra would have provided greater benefit if given for a longer period. The favorable changes seen within a short time frame suggest that the benefits of anakinra are not due to changes in myocardial structure but rather due to changes in the function/compliance of the heart, vasculature and/or the skeletal muscles.[7,8] IL-1 inhibits contractility, lusitropy, and beta-adrenergic responsiveness within few hours of administration.[10,16] We cannot exclude, however, that a longer treatment with anakinra may provide more favorable changes due to a combined effect on function and structure (i.e hypertrophy or fibrosis). Moreover, inflammation appears also to regulate oxygen transport and utilization in skeletal muscle.[24]

There are several limitations to the D-HART pilot study, primarily the small number of patients and short duration of treatment and observation. All but one patient in this pilot study were women, the majority of patients were self-defined African-Americans, all were obese and all were affected by systemic arterial hypertension. While these characteristics are common to many HFpEF study populations, the generalizability of the results to other patients may be limited. The lack of BNP levels elevation in many subjects despite impaired diastolic function and moderate-to-severe limitations at CPX fits well with the paradigm of a

lower BNP levels in HFpEF, a relative deficit in BNP elevation especially in obese patients with HFpEF, and a lack of correlation of changes in pro-BNP and outcomes in HFpEF.[25_27] The choice to use CRP as a screening tool and exclude patients with CRP≤2 mg/l may also appear to be arbitrary, and we cannot exclude that such patients would have equally benefited from anakinra treatment. Nevertheless, for this pilot study, we chose CRP>2mg/l as it appears to be a validated cut-off to identify a subgroup of patients at greater risk and a target for treatment.[28_29] Moreover, it is impossible to know whether a longer duration of treatment would have provided more favorable effects or unforeseen intolerance to the treatment. Future studies are needed in this area.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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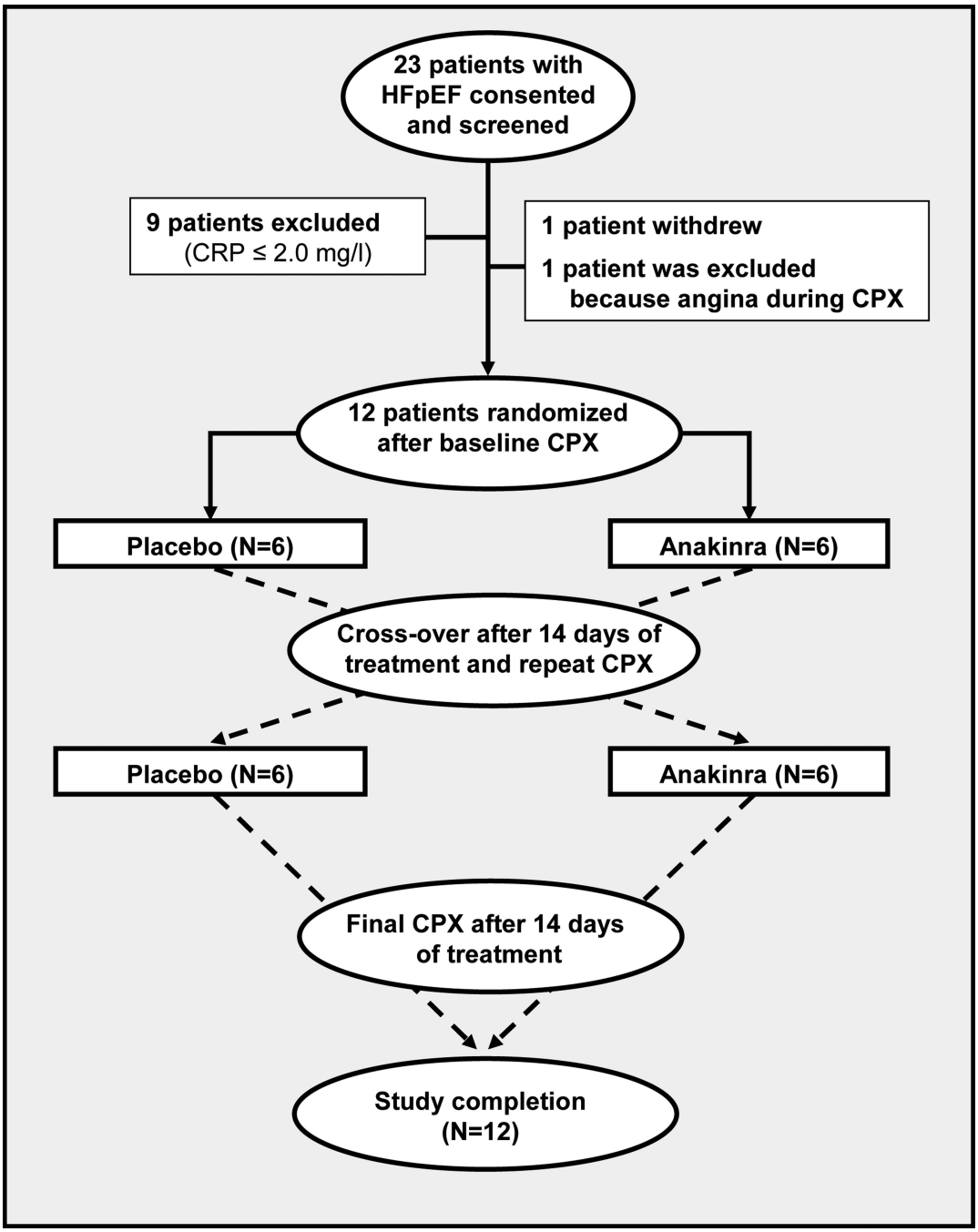

FIGURE 1. Study design

Schematic diagram of the study design and the enrollment process.

Abbreviations: CPX= cardiopulmonary exercise testing; CRP= C reactive protein; HFpEF= Heart failure with preserved ejection fraction.

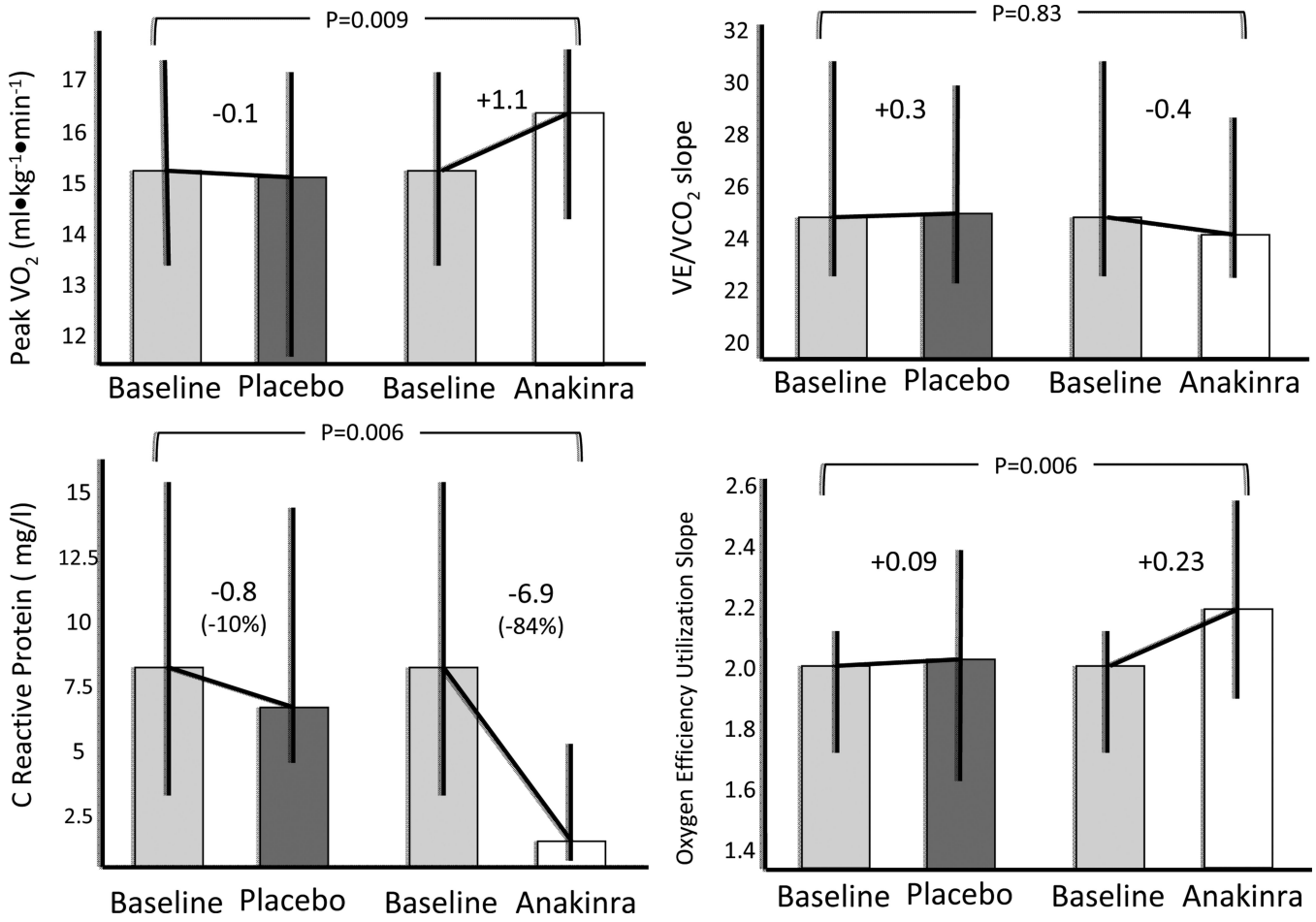

FIGURE 2. Effects of IL-1 blockade with anakinra on exercise parameters and C-reactive protein plasma levels

The figure shows interval changes in the peak oxygen consumption (VO_2 – top left panel), C reactive protein plasma levels (CRP – bottom left panel), ventilatory efficiency (VE/VCO_2 – top right panel), and oxygen utilization efficiency slope (OUES – bottom right panel) after placebo and anakinra treatment phases.

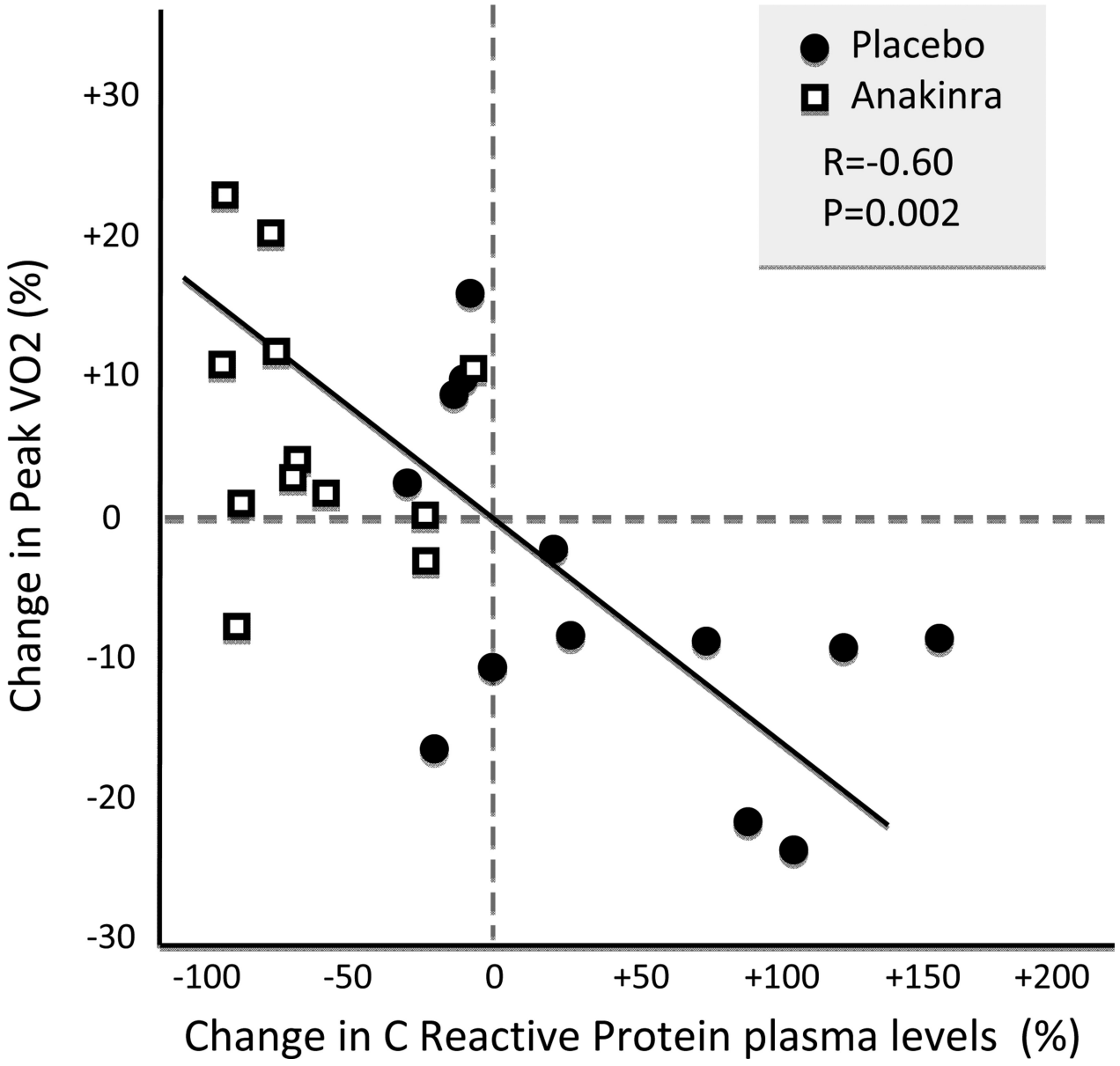

FIGURE 3. C reactive protein levels

Correlation between the changes in C-reactive protein (CRP) plasma levels with treatment and the effects on aerobic exercise capacity (peak oxygen consumption [VO_2]).

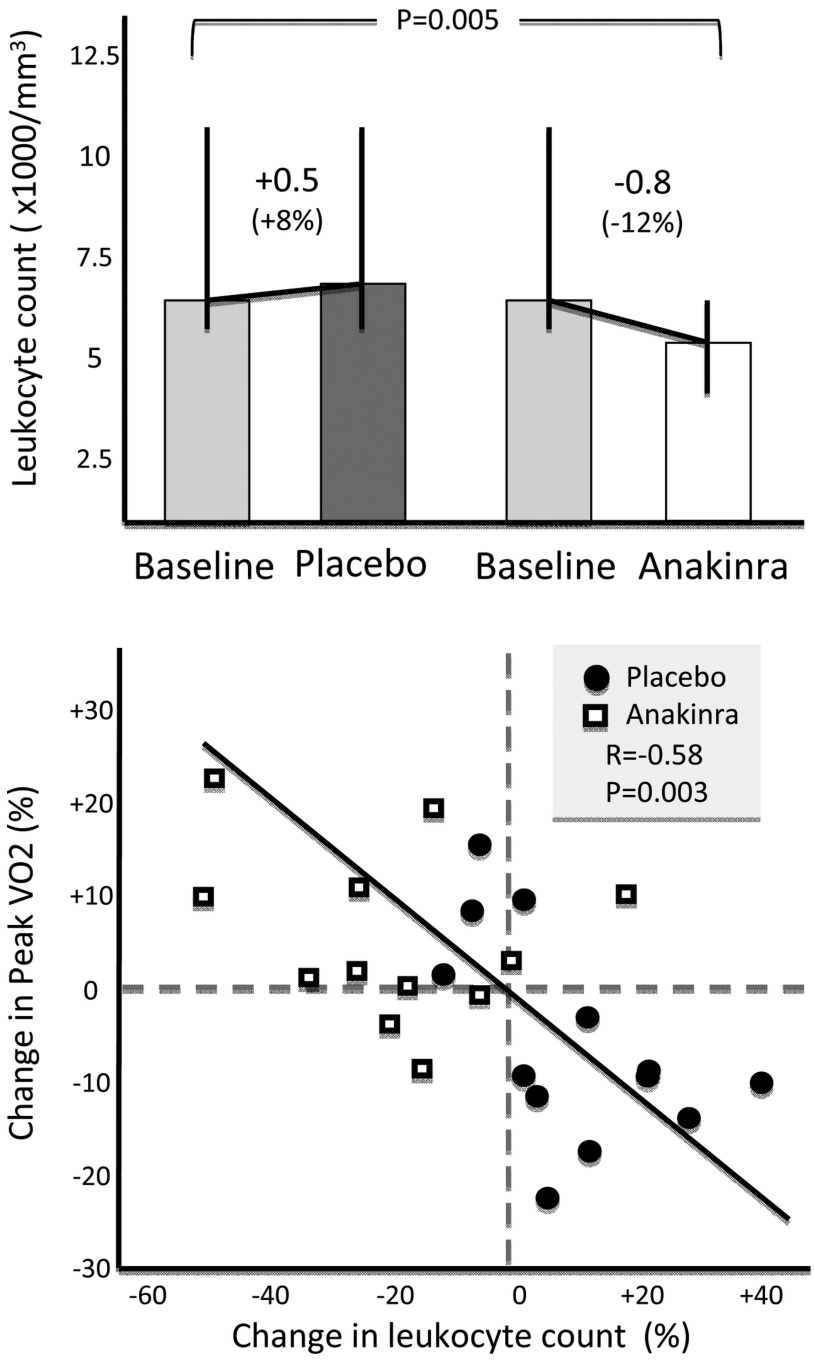

FIGURE 4. Leukocyte count

Changes in blood leukocyte count and changes in peak oxygen consumption (peak VO_2) after treatment.

Table 1

Baseline clinical characteristics and placebo-corrected changes in peak VO_2

	Age (yrs)	Gender	Ethnicity	Hypertension	Diabetes	NYHA Class	BNP	hs-CRP	LVEF	LVEDVi	LVMi	E/E′	LVEDP	Peak VO_2	V_E/VCO_2	OUES	Change in peak VO_2
#1	40	F	C	Y	N	2	43	4.7	63	33	72	24	n/a	16.9	24.6	2.08	+1.9
#2	52	F	AA	Y	N	2	8	9.9	63	43	131	8	n/a	20.5	23.2	2.21	−1.1
#3	55	F	AA	Y	Y	3	39	3.5	57	59	123	11	18	16.2	30.6	1.79	+1.7
#4	55	F	AA	Y	N	2	19	6.6	58	33	91	11	n/a	18.7	22.3	2.85	−1.0
#5	57	F	AA	Y	Y	2	2	17.0	57	41	79	11	17	14.1	25.2	2.12	+3.0
#6	60	F	AA	Y	Y	3	25	11.5	60	62	125	15	n/a	13.8	24.9	1.92	−0.7
#7	62	F	C	Y	Y	3	39	5.0	64	37	68	11	34	16.1	29.6	2.54	+2.1
#8	63	F	AA	Y	N	2	11	15.2	74	34	89	21	20	14.4	22.2	1.8	+0.4
#9	64	F	C	Y	Y	3	112	2.6	53	40	78	10	n/a	13.1	33	1.34	+1.7
#10	64	F	AA	Y	Y	3	131	15.5	67	41	90	20	n/a	11.4	21.1	2.02	+3.5
#11	65	M	C	Y	Y	2	23	3.1	59	60	68	11	n/a	17.3	31.1	1.73	+3.0
#12	70	F	AA	Y	N	3	414	18.2	51	78	100	19	15	9.4	45.4	1.22	+1.8

Abbreviations: AA=African-American; BNP=Brain natriuretic peptide (pg/ml) ; C=Caucasian; E/E′= ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity; F=female; hs-CRP=high sensitivity C-reactive protein (mg/l); LVEDVi=left ventricular end-diastolic volumeindex (ml/m^2); LVEF=left ventricular ejection fraction (%); LV Mass index=left ventricular mass index (g/m^2); M=male; N=no; n/a=not available; NYHA Class=New York Heart Association functional classification system for heart failure; OUES= Oxygen-uptake efficiency slope; Peak VO_2=maximal oxygen consumption during cardiopulmonary exercise testing (ml•kg^{-1}•min^{-1}); VE/VCO_2=ventilatory equivalent ratio for carbon dioxide; Y=yes.