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Angiotensin II blockers in obstructive pulmonary disease.

A randomized, controlled trial

Stefan Andreas, Christoph Herrmann-Lingen, Tobias Raupach, Lars Lüthje, Jan A Fabricius, Nadine Hruska, Wolfgang Körber, Birgit Büchner, Carl-Peter Criée, Gerd Hasenfuß, Peter Calverley.

Lungenfachklinik Immenhausen (SA)

Dept. of Cardiology and Pneumology, Georg-August-Universitat Göttingen, Germany (SA, TR, LL, NH, GH)

Dept of Psychosomatics and Psychotherapy, section of Psychocardiology; Georg-August-Universitat Göttingen, Germany (CHL, BB)

Bereich Pneumologie Evangelisches Krankenhaus Göttingen Weende e.v., Germany (WK, CPC)

Department of Medicine, University Hospital Aintree, Liverpool, UK. (PC)

Short title: Irbesartan in COPD

ADDRESS FOR CORRESPONDENCE Professor Dr. S. Andreas, Lungenfachklinik Immenhausen, Robert-Koch-Str. 3, 34376 Immenhausen, Germany. phone: +49 5673 501-111, fax: +49 5673 501-101, e-mail: sandreas@med.uni-goettingen.de

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Abstract

In COPD, the sympathetic nervous system as well as the renin-angiotensin system is activated with possible negative systemic effects on skeletal muscles. Angiotensin II type 1 receptor blockers inhibit the sympathetic and renin-angiotensin systems and might improve skeletal and respiratory muscle strength in patients in whom these systems are activated.

We evaluated the effects of the angiotensin receptor blocker irbesartan given over 4 months to 60 patients with COPD and an FEV1 < 50% predicted without obvious cardiovascular disease that would necessitate the administration of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker.

Irbesartan was well tolerated, but did not exert a significant effect on the primary endpoint maximum inspiratory pressure. Spirometry was not affected but total lung capacity was reduced. Irbesartan led to a significant decrease in hematocrit (46.4 ± 3.6 to 43.9 ± 4.3% vs. 47.5 ± 2.4 to 48.7 ± 3.0 with placebo; p ANOVA < 0.0005).

In conclusion respiratory muscle strength in COPD patients was not influenced by angiotensin II receptor blockade. However, the changes in hematocrit and total lung capacity following irbesartan raise the possibility that well known cardiovascular drugs can produce unanticipated beneficial effects in COPD patients.

word count: 194

Key words: chronic obstructive lung disease, hematocrit, irbesartan, respiratory muscle

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of death and disability worldwide, and the burden of this disorder will continue to increase in the coming decades [1]. Treating COPD improves lung function, yet this is unlikely to slow the steady downhill course of the disease or even reduce mortality [1,2]. The pathophysiology of COPD is not limited to the lungs. Indeed, COPD has been identified as having a systemic or muscle component [3,4].

In COPD, the sympathetic nervous system as well as the renin-angiotensin system is activated [5-7] with potentially negative systemic effects, for example on the skeletal muscles. Angiotensin II type 1 receptor (AT1) blockers inhibit the sympathetic and renin-angiotensin systems [8] and improve both the quality of life and longevity in patients with heart failure. The AT1 blocker irbesartan prevents the development of muscle atrophy in a rat model of right heart failure [9]. Moreover, in patients with left heart failure, maximum inspiratory pressure improved after treatment with angiotensin-converting enzyme inhibition [10].

Activation of the renin-angiotensin system is associated with the development of secondary erythrocytosis in hypoxemic patients with COPD [11,12]. Furthermore AT II type 1 receptors are highly expressed within the lung [13] and modulate alveolar epithelial cell apoptosis [14] and lung fibroblast growth [15]. Thus, there is the possibility that AT1 blockers effect hematocrit and lung function in COPD. The effects of AT1 blockade in patients with COPD have never been thoroughly investigated. Although cardiovascular comorbidity is common in patients with COPD and hence cardiovascular drugs are often used, there is only sparse data about the pulmonary and systemic effects of cardiovascular drugs in patients with COPD [16].

Thus, several reasons point to a potential benefit of AT1 blockers in COPD. Therefore, we did a randomised controlled trial of AT1 blockade in order to uncover possible clinical benefits and to provide pilot data for subsequent larger studies.

Methods

Study design

This study was a randomized, placebo-controlled, double-blinded trial. Inclusion criteria were COPD patients on stable treatment (medication, supplemental oxygen and noninvasive ventilation) for at least 4 weeks with an FEV1 lower than 50% predicted and an age of 30 to 80 years. Patients already treated with an ACE-inhibitor or an AT1-blocker were excluded, as were patients with any conventional indication for these drugs. Further exclusion criteria were known allergies to the study drug, chronic heart failure, untreated arterial hypertension, myocardial infarction within the last 6 months, dehydration, symptomatic hypotension, increased serum potassium, and renal artery stenosis > 70%.

The study was approved by the local institutional ethics committee, and informed written consent was obtained from all patients before enrollment in the protocol.

Study protocol

Patients were recruited in cooperation with four local chest physicians. At the baseline visit, a physical examination including measurement of heart rate and blood pressure, together with measurements of spirometry, respiratory muscle strength, arterial blood gas analysis, electrocardiogram, Holter-ECG for 20 min at rest, quadriceps muscle strength, echocardiography and exercise testing. Blood samples were collected for evaluation of hematology, liver and renal function as well as epinephrine, norepinephrine, aldosterone, renin, endothelin-1, atrial natriuretic peptide, interleukin-10, and leptin as described previously [17]. In addition, the patients completed two health status questionnaires. Patients were then dispensed either 150 mg/d irbesartan or an identical placebo once a day, treatment being randomly assigned by sealed envelopes. Blood pressure was measured before and 6 hours after administration of the study drug. After one month, the dose of the study drug

was increased to 300 mg/d under blood pressure control. After further three months, the patients were re-examined and underwent the same tests as in the baseline examination. Individual compliance was evaluated by counting the number of tablets on the second and third visit. Patients were interviewed by telephone about side effects and changes in medication, supplemental oxygen and noninvasive ventilation at two and three months after the first visit.

Lung function testing

Spirometry was performed and lung volumes were evaluated by body plethysmography (master lab, Jäger, Würzburg, Germany) [18]. The maximum static inspiratory pressure that a subject can generate at the mouth was measured at least five times at the residual volume, and the best trial was registered [19,20].

Heart rate, exercise testing, echocardiography

Mean heart rate was derived from the 20 min Holter tracing. A symptom-limited exercise test on a cycle ergometer was performed [21]. The load was increased by 15 Watts every three minutes (Variobike 550, Ergoline GmbH, Germany). Transthoracic echocardiography was performed by a single experienced investigator (WK) [22].

Quality of life

Quality of life was evaluated by different standardized questionnaires: the German version of the St. George's Respiratory Questionnaire [23] and a questionnaire to evaluate the profile of quality of life of psychically ill persons [24].

Statistical analysis

Based on our own as well as published data [10], we expected to detect a difference of 0.4 kPa in the primary endpoint, maximum inspiratory pressure, with a power of 80% and a significance level <0.05 in a two-tailed test with 30 patients in each group and a drop out rate of 10%. The statistical analysis was performed with SPSS 11.5 for Windows. Randomization success for baseline parameters was assessed by Students' t tests for independent samples, Mann-Whitney U tests or chi-square tests, depending on type and distribution of data. Repeated–measures analysis of variance (ANOVA) with time as within-groups factor and the time by treatment interaction was used to analyze the effects of treatment. If the requirements for performing the ANOVA were not met, nonparametric tests (Wilcoxon or McNemar) were employed instead. For the two prespecified secondary endpoints (total lung capacity and hematocrit) Bonferroni correction was used to adjust for multiple testing. Two-tailed tests were used and significance was accepted at a value of $p<0.05$.

Results

Subjects

Of the 225 patients screened for inclusion in the study, most were excluded since they were either already receiving an angiotensin-converting enzyme inhibitor or suffered from chronic heart failure (Figure 1). Of the 60 patients included, 51 used inhalers containing β_2-sympathomemetic drugs. Inhaled anticholinergic agents or corticosteroids were used by 34, and 28 patients, respectively. Oral medications included corticosteroids taken by 28 and theophylline taken by 42 patients. Subject characteristics and baseline lung function tests were comparable between the two groups, although the treatment group was significantly shorter (Table 1). Values for creatinine, alanine aminotransferase, aspartate aminotransferase, bilirubin, fibrinogen, epinephrine, IL-10, were similar in both groups (data not shown).

Non-invasive ventilation was used by 10 patients at least during their sleep. Long-term oxygen therapy was used by 20 patients for about 15 – 18 hours a day. Seventeen patients were current smokers. Sinus rhythm was found in 58 and atrial fibrillation in 2 patients. A right bundle branch block was diagnosed in 15 patients. Past medical history, physical examination, ECG recordings, laboratory investigations pharmacological as well as non-pharmacological treatment revealed no significant difference between the groups at baseline (data not shown).

Lung function tests

After 4 months of treatment, irbesartan had not exerted a significant effect on the primary endpoint, maximum inspiratory pressure (Table 2). Irbesartan did not effect spirometry but total lung capacity fell (Table 2). The p value following Bonferroni correction for the secondary outcome variable total lung capacity as % predicted was 0.025. There was a trend towards a lower RV/TLC ratio ($p = 0.075$, ANOVA for time by treatment interaction) and a

higher FEV1/VC ratio (p = 0.072, ANOVA for time by treatment interaction). Vital capacity, PaO_2, $PaCO_2$ and body weight remained unchanged.

Blood pressure, exercise testing, echocardiogram

Following irbesartan, there was a significant decrease in systolic blood pressure measured in the morning (Table 3), whereas no significant change was seen in the placebo group. However, the time by treatment interaction factor by ANOVA revealed no significance.

Irbesartan had no significant effect on maximal workload and other parameters of the exercise test (Table 3). ECG findings also remained unchanged. Echocardiography revealed no significant changes in left ventricular end-diastolic and end-systolic diameters and thus no effect on ejection fraction (Table 3). There was a reduction in right ventricular diameter in the placebo but not the irbesartan group.

Post hoc power calculations revealed that the study was underpowered to detect modest changes in maximal oxygen uptake at exercise and quadriceps strength.

Hematocrit and humoral effects

Irbesartan led to a significant decrease in hemoglobin and hematocrit (Table 4; Figure 2). The p value following Bonferroni correction for the secondary outcome variable hematocrit was 0.0005. Baseline hematocrit levels and the magnitude of the decrease following administration of irbesartan were non –significantly related (r = 0.34; p = 0.09). In none of the patients treated with irbesartan, did hematocrit fall below 30%.

Irbesartan did not effect epinephrine, norepinephrine, endothelin-1, atrial natriuretic peptide, activity of the angiotensin converting enzyme, interleukin-10, or leptin. Irbesartan led to a rise in plasma renin concentration from 38.0 mU/ml (range 3 – 500 mU/ml) to 367.0 mU/ml (range 48 – 500 mU/ml; p < 0.001). Since placebo did not affect this parameter (baseline 39 mU/ml; range 9 – 500 mU/ml; after 4 months 44.0 mU/ml; range 7 – 500 mU/ml; p = 0.8),

there was a significant difference in plasma renin concentration between the two groups at the end of the study ($p < 0.001$). A decrease in aldosterone levels was observed both in the irbesartan group (from 11.0 ng/dl, range 0.75 - 120.0 ng/dl to 5.0 ng/dl, range 0,75 - 113.0 ng/dl; $p < 0.05$) and the placebo group (from 8.5 ng/dl, range 0.75 – 120.0 ng/dl to 3.1 ng/dl, range 0.75 - 25.0 ng/dl; $p < 0.05$). Potassium levels differed between the two groups at the beginning of the study and showed no significant change over the 4-month period. Serum sodium concentrations increased in patients receiving placebo while they remained constant in patients receiving irbesartan (Table 4).

Safety, side effects, Quality of life

Treatment with bronchiodilatators, corticosteroids, supplemental oxygen or noninvasive ventilation was not significantly impacted by study medication. Irbesartan had no significant effect on creatinine, bilirubin or fibrinogen. We found a significant rise in alanine aminotransferase levels (Table 4) while aspartate aminotransferase showed no significant difference (ANOVA for time by treatment interaction).

Evaluation of the questionnaires revealed no difference between the two groups concerning side-effects. At the first follow-up appointment, a total of 19 patients complained about side-effects, whereas at the second follow-up appointment only 6 patients reported such effects.

Quality of life, as measured by the questionnaires was low in both groups (Table 5). As for the St. George's Respiratory Questionnaire, the placebo group scored significantly higher (i.e. worse) than the irbesartan group regarding the total score as well as the subscales “symptoms” and “activity” at baseline (all $p < 0.01$). However neither group changed significantly during the course of the study.

Discussion

Although commonly used, there is only sparse evidence of any pulmonary and/or systemic effects of cardiovascular drugs in patients with COPD [16]. Angiotensin-converting enzyme inhibitors often induce cough, and acute bronchospasm is a rare but serious adverse reaction [16]. For ß-blockers there is some evidence of increased airway resistance in COPD patients [16]. Diuretics have not been investigated in patients with COPD but have theoretical risks such as alkalosis [16].

In this study we hypothesized that the properties of one class of cardiovascular drugs, the AT1 blockers, would be valuable in COPD patients. We found that our primary endpoint, maximum inspiratory pressure was not affected by irbesartan, the AT1 blocker we used, despite evidence that it was biologically active in the doses given. However, irbesartan did reduce the hematocrit and was well tolerated.

Skeletal muscle function and inspiratory pressure

Our study rationale came from observations that in COPD, the sympathetic nervous system and the renin-angiotensin system (RAS) are activated [5-7,25] with a well described interaction between both systems [26,27]. Sympathetic nervous system activation is associated with impaired endothelial function and decreased exercise-induced vasodilatation in skeletal muscle, a decrease in the number of type 1 (slow, endurance) muscle fibers, cardiomyocyte injury and apoptosis and catabolic/anabolic imbalance with muscle wasting and lipolysis [28,29].

Genetic studies suggest that in healthy subjects increased angiotensin-converting enzyme activity with high angiotensin II plasma levels mediate greater strength gains perhaps via muscle hypertrophy whereas lower angiotensin II levels mediate enhanced endurance performance perhaps via changes in substrate availability, muscle fiber type and efficiency (for review see [27]). A reduction in angiotensin-converting enzyme activity reverses the decline of peripheral muscle performance in patients with congestive heart failure [27]. In a rat model of right heart failure, the AT1 blocker irbesartan prevented the development of apoptosis-

dependent muscle atrophy [9]. Moreover, in patients with left heart failure, maximum inspiratory pressure was improved by angiotensin-converting enzyme inhibition in an uncontrolled study [10].

Thus, it seemed reasonable to suggest that AT1 blockers might effect endurance performance of skeletal and respiratory muscle function in COPD patients. In the present study, we were unable to demonstrate an improvement in maximal inspiratory pressure or maximal quadriceps muscle strength. Other methods that better reflect endurance performance of the diaphragm or the quadriceps might have been more appropriate to detect the hypothetical effects of the study drug. However our data suggest that more specific measures to identify patients with the greatest activation of the sympathetic and RAS systems will be needed before this intervention can be rigorously tested, as an effect was not seen in a reasonable number of COPD patients who might reasonably be thought to exhibit this activation.

Hematocrit

Plasma renin activity and aldosterone plasma concentrations are elevated in patients with COPD [7,25]. The activation of the renin-angiotensin system is particularly pronounced in patients with secondary erythrocytosis [12], and angiotensin II enhances erythropoietin-stimulated erythroid proliferation in vitro [11]. Accordingly losartan, an AT1 blocker, reduced hematocrit in patients with hypoxemic COPD and secondary erythrocytosis in a previous uncontrolled study [30]. We now extend these findings, reporting a similar effect of irbesartan in a controlled trial in patients with COPD without frank erythrocytosis. There was a trend towards a larger fall in hematocrit in the patients with high baseline hematocrit. Interestingly, AT1 blockade did not affect hematocrit in patients with chronic heart failure, who also have an activated renin-angiotensin system but in whom hypoxaemia, by day or internmittently at night, is not an important clinical problem.

Anemia is present in some COPD patients with cachexia and might be aggravated by AT1 blockade. This might impair oxygen delivery, cause cardiac output to increase and thus impair right heart function and ultimately cause right heart failure. However, anemia with a hematocrit below 30% was not noticed in our study. On the other hand erythrocytosis is related to cardiovascular disease, especially myocardial infarction, independent of other risk factors such as smoking [31,32]. Thus, it is conceivable, albeit speculative, that adjunctive AT1 blockade in a small but well- defined subgroup of COPD patients reduces cardiovascular morbidity by reducing erythrocytosis. Besides, before performing phlebotomy in patients with COPD, an AT1 blocker can be tried.

Lung function

In our study, there was no significant effect on spirometry. However, irbesartan led to a decrease in total lung capacity, while there was a trend towards an increase in the placebo group. This finding is difficult to explain and should not be overemphasized, since it was not the primary endpoint, and the significance found in the time by treatment interaction was due partly to the changes observed in the placebo group.

In patients with bronchial asthma, AT1 receptor blockade slightly reduced bronchial hyperresponsiveness to metacholine [33]. In the COPD patients studied here, we did not notice an effect on FEV1 or airway resistance.

Since there was a trend towards a reduction of the residual volume / total lung capacity ratio, and since FEV1, PO_2, and exercise capacity were not impaired, it is also unlikely that the reduction in total lung capacity was due to restrictive lung disease by e.g. pulmonary fluid accumulation.

Indeed, recent genetic data presented by Hopkinson et al. are consistent with an effect of AT1 blockade on lung function [34]. In COPD patients with the DD genotype i.e. homozygous for deletion of the angiotensin-converting enzyme gene (which causes markedly increased

angiotensin II activity at the receptor level), functional residual capacity was significantly higher [34].

Blood pressure, heart rate and side effects

There was a drop in systolic blood pressure of about 6 mmHg following irbesartan that was insignificant when compared to placebo. This minor effect on blood pressure is comparable to previous studies in patients with an activated renin-angiotensin system due to heart failure and normal blood pressure [35].

The increase in plasma renin activity following irbesartan in our patients was expected and provides an indirect measure of compliance with treatment. In healthy subjects and patients with arterial hypertension, renin and angiotensin II increased while aldosterone did not change significantly following irbesartan administration [36,37]. In our patients, we noticed a reduction in serum sodium that can be explained by the promotion of urinary sodium excretion by AT1 blockade [38] in the presence of impaired sodium excretion in patients with severe COPD [39].

As in former large studies on patients with renal diseases, the study drug was well tolerated [40]. In our patients, the incidence of side-effects was similar to placebo. However, alanine aminotransferase activity increased slightly, an effect that has not been seen in the previous large studies on AT1 blockade.

Limitations

Randomization yielded an irbesarten group with significantly lower baseline serum potassium levels, lower height as well as a trend towards lower maximal inspiratory pressures. However, the statistical method used (ANOVA with time by treatment interaction) takes differences in baseline characteristics into account. The small sample size and inhomogeneous cohort (concerning age, sex, size, pharmacotherapy, respiratory support) does not allow us to firmly exclude a significant effect of AT1 blockade on respiratory muscle strength and give exact

power calculations. Especially age has a profound impact on muscle function and disease progression.

In conclusion, angiotensin II receptor blockade did not improve respiratory muscle strength or exercise capacity, but was otherwise well tolerated in patients with COPD stage III and IV. The reduction in hematocrit following irbesartan might be disadvantageous or beneficial depending on baseline hematocrit. This and the impact on total lung capacity, also hinted at in the previous genetics data, deserve a prospective investigation. Our data indicate that cardiovascular drugs commonly used to treat co-morbidities in COPD patients can have subtle and unanticipated effects. Developing appropriate methodologies to test these interactions is an important challenge for future research.

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Figure legends

Figure 1: Screening, enrolment, allocation and follow-up of patients

Figure 2: Effects of placebo and irbesartan on hematocrit. Base indicates baseline; 4 mo, follow-up at 4 months

Tables

TABLE 1. Subject Characteristics and Baseline Conditions

	Placebo	Irbesartan	*P*
Sex, M/F	23/7	20/10	0.39
Age, years	60.0 ± 7.7	62.8 ± 8.5	0.54
Height, cm	174 ± 8.2	169 ± 6.5	0.02
Weight, kg	74.4 ± 15.3	71.7 ± 14.5	0.43
Body mass index, kg/cm^2	24.5 ± 3.7	25.1 ± 4.7	0.59
FEV_1 / vital capacity, %	41.7 ± 11.2	42.7 ± 10.3	0.73
FEV_1, % predicted	30.6 ± 8.3	32.9 ± 9.1	0.13
Vital capacity, % predicted	57.8 ± 12.2	63.4 ± 13.1	0.37
RAWtot, kPa/l/s	0.77 ± 0.6	0.65 ± 0.4	0.26
Left ventricular ejection fraction, %	64 ± 10	63 ± 8	0.72
Sodium, mmol/l	140.6 ± 2.5	140.1 ± 3.0	0.48
Potassium, mmol/l	3.9 ± 0.4	4.2 ± 0.5	0.009
Norepinephrine,	686 ± 458	624±419	0.59

FEV_1, forced expiratory volume in 1 second; RAWtot, total airway resistance.
Data are expressed as Mean ± SD.

TABLE 2. Lung function tests

	Placebo		Irbesartan		
	Baseline	4 months	Baseline	4 months	P_{int}
Pimax, kPa	5.5 ± 2.0	5.8 ± 2.2	4.8 ± 1.9	4.5 ± 2.0	0.16
P01max, kPa	3.3 ± 1.0	3.4 ± 1.7	2.9 ± 1.0	2.7 ± 1.3	0.47
FEV_1 / vital capacity, %	42 ± 12	38 ± 11	40 ± 7	43 ± 13	0.07
Vital capacity, l	2.3 ± 0.7	2.5 ± 1.0	2.3 ± 0.7	2.1 ± 0.7	0.18
FEV_1, l/s	0.95 ± 0.3	0.95 ± 0.6	0.91 ± 0.3	0.87 ± 0.3	0.67
RAWtot, kPa/l/s	0.79 ± 0.59	0.64 ± 0.4	0.67 ± 0.4	0.69 ± 0.5	0.14
Total lung capacity, % predicted	110.4 ± 23	121.7 ± 25.8 *	119.7 ± 16	113.7 ± 19.2	0.01
Residual volume / Total lung capacity, %	66.2 ± 11.0	70.4 ± 10.3 *	68.9 ± 7.2	68.8 ± 7.3	0.08
pO_2, mm Hg	64.4 ± 10.4	62.5 ± 11.8	65.7 ± 10.4	66.7 ± 12	0.31
pCO_2, mm Hg	43.3 ± 3.4	44.3 ± 3.7	42.9 ± 3.6	42.8 ± 3.5	0.45
Quadriceps maximal muscle strength, kg	22.1 ± 9.1	22.3 ± 9.8	19.6 ± 8.6	21.6 ± 9.3	0.18
Weight, kg	76.0 ± 15.1	76.1 ± 16.8	71.3 ± 14.9	72.2 ± 14.8	0.51

FEV_1 indicates forced expiratory volume in 1 second; P01max indicates maximal mouth occlusion pressure at 0.1 sec.; P_{int}, ANOVA for time by treatment interaction. For correction for multiple comparisons see text. Values are given as Mean ± SD.
*P ANOVA for time <0.05.

TABLE 3. Cardiovascular Parameters

	Placebo		Irbesartan		
	Baseline	4 months	Baseline	4 months	P_{int}
Systolic blood pressure, mmHg	129.8 ± 14.6	129.1 ± 15.5	131.0 ± 14.7	124.4 ± 16.1 *	0.26
Diastolic blood pressure, mmHg	79.0 ± 7.8	77.6 ± 8.0	78.7 ± 9.2	75.5 ± 9.1	0.45
Heart rate, bpm	88.8 ± 13.1	87.3 ± 21.4	82.5 ± 10.6	83.2 ± 17.0	0.68
LVEDD, mm	43.1 ± 9.0	46.5 ± 7.7	44.3 ± 7.5	45.4 ± 6.9	0.4
LVESD, mm	28.6 ± 8.0	26.8 ± 6.7	30.1 ± 7.1	29.1 ± 8.5	0.79
RVED, mm	36.7 ± 5.9	33.6 ± 4.7	33.3 ± 5.4	33.1 ± 5.6	0.05
Max. heart rate, bpm	124 ± 15	120 ± 19	128 ± 15	125 ± 16	0.62
Max. minute ventilation, L/min	28.3 ± 8.9	28.6 ± 14.1	29.2 ± 12.2	29.3 ± 12.1	0.89
VE/VCO2 slope	25.6 ± 10.4	23.4 ± 16.1	25.1 ± 11.7	24.1 ± 14.3	0.81
Max. respiratory quotient	1.00 ± 0.08	1.00 ± 0.07	1.05 ± 0.12	0.96 ± 0.15	0.09
Max. O_2 uptake, ml/min	957 ± 286	885 ± 433	989 ± 442	986 ± 411	0.41

LVEDD indicates left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; RVED, right ventricular end-diastolic diameter; VE/VCO2 ventilation / CO2 production; P_{int}, ANOVA for time by treatment interaction. Data are expressed as Mean ± SD. *P ANOVA for time <0.05

TABLE 4. Blood Tests

	Placebo		Irbesartan		
	Baseline	4 months	Baseline	4 months	P_{int}
Hematocrit, %	47.5 ± 2.4	48.7 ± 3.0	46.4 ± 3.6	43.9 ± 4.3 **	0.0001
Hemoglobin, g/dl	15.7 ± 0.9	15.9 ± 1.1	15.1 ± 1.3	14.2 ± 1.6 **	0.002
Sodium, mmol/l	140.1 ± 2.5	142.1 ± 3.2 *	140.2 ± 3.0	140.2 ± 3.0	0.021
ALT, U/l	24.2 ± 14.4	22.3 ± 13.4	18.1 ± 10.2	22.0 ± 9.9 *	0.047

ALT indicates alanine aminotransferase; Pint ANOVA for time by treatment interaction. For correction for multiple comparisons see text. Values are given as Mean ± SD. *P ANOVA for time <0.05, **P ANOVA for time <0.001

TABLE 5. Quality of life

	Placebo		Irbesartan	
	Baseline	4 months	Baseline	4 months
PLC total score	1.9 ± 0.6	2.0 ± 0.9	1.9 ± 0.5	1.8 ± 0.8
PLC item "negative mood"	2.9 (1.6-3.1)	3.7 (2.0-2.4)	2.6 (1.3-3.1) †	3.5 (0.6-4.0)
SGRQ total score	63.4 (25.5-89.8)	52.5 (11.4-84.4)	44.0 (24.6-73.8) **	47.8 (27.0-73.6)
SGRQ item "symptoms"	65.31 (17.9-102.0)	50.0 (14.3-93.9)	42.9 (12.2-102.0) *	44.9 (20.4-102.0)
SGRQ item "activity"	66.67 (40.7-92.6)	64.0 (0-100)	51.9 (26.9-92.3) *	56.6 (37.0-73.1)

PLC indicates profile of quality of life of psychically ill persons; SGRQ, St. George's Respiratory Questionnaire. Values are given as mean ± SD or median (range). * P placebo vs. irbesartan at baseline < 0.05; ** P placebo vs. irbesartan at baseline < 0.01; † P Wilcoxon for time < 0.05

Figures

Figure 1

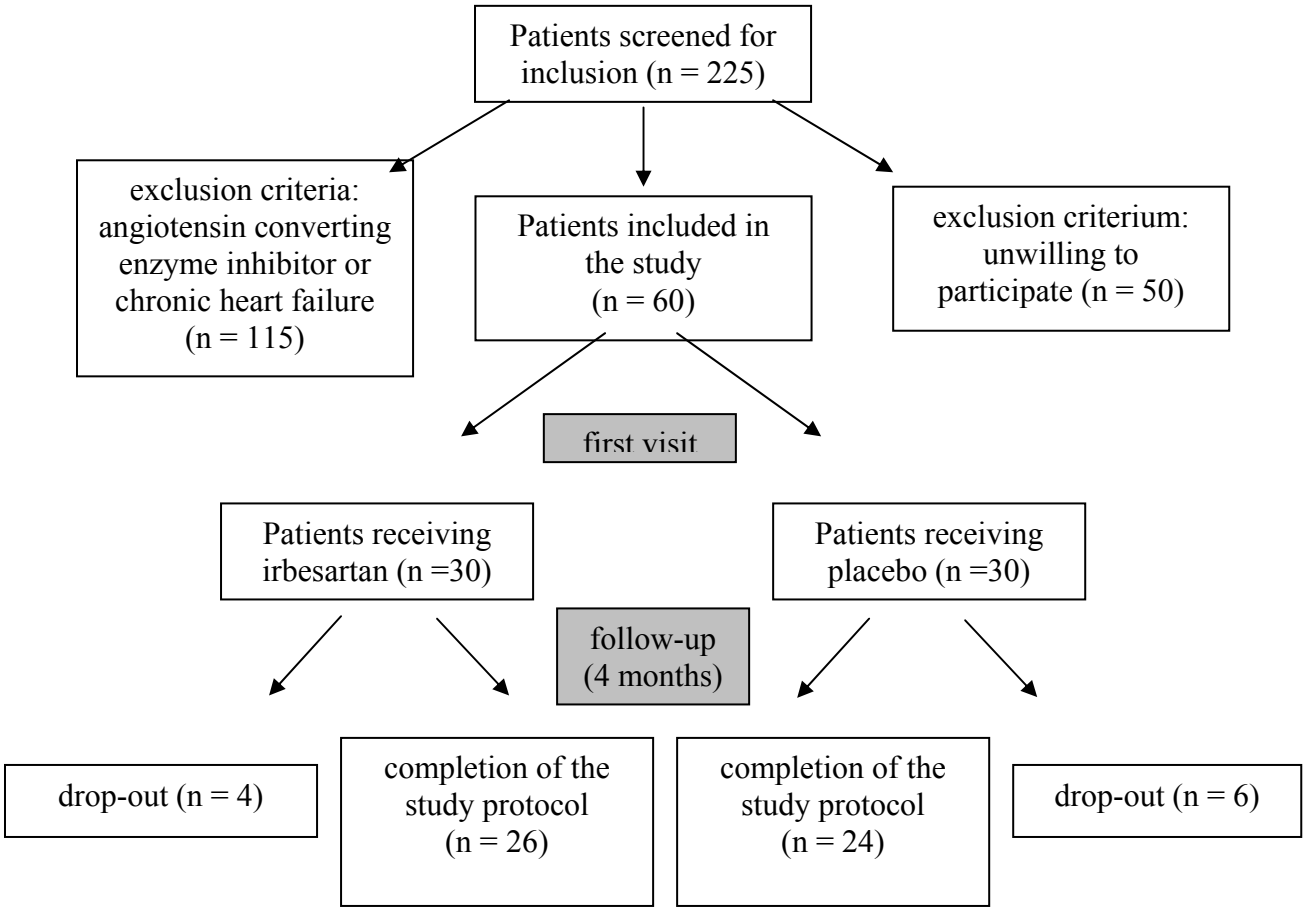
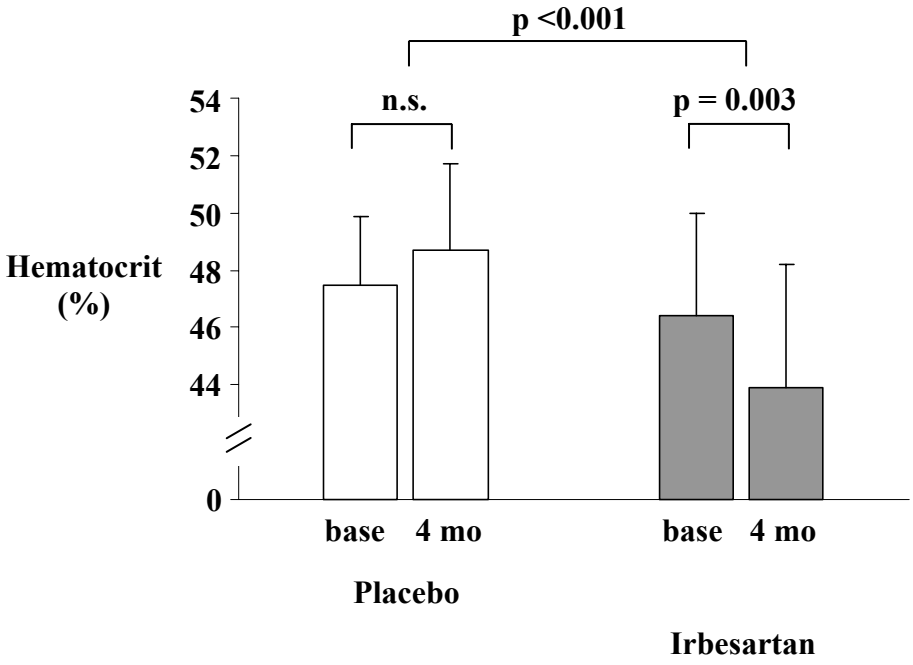


Figure 2


p <0.001
n.s.
p = 0.003
54
52
50
48
46
44
0
Hematocrit (%)
base
4 mo
base
4 mo
Placebo
Irbesartan