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Clinical research

Spironolactone improves lung diffusion in chronic heart failure

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Aims To evaluate whether anti-aldosteronic treatment influences lung diffusion (DLCO) in chronic heart failure (HF) patients. Spironolactone improves clinical conditions and prognosis in chronic HF and reduces connective tissue matrix turnover; DLCO abnormalities in chronic HF are related to increase in fibrosis and connective tissue derangement.

Methods and results Thirty stable chronic HF patients, with reduced DLCO (<80% of predicted), were randomly assigned to active treatment (25 mg spironolactone daily) or placebo in addition to conventional anti-failure treatment. They were evaluated by quality of life questionnaire, laboratory investigations, cardiopulmonary exercise test, and pulmonary function test, which included DLCO and membrane diffusing capacity (DM). The evaluation was done before treatment and 6 months after. Quality of life score and standard pulmonary function tests were not significantly affected by spironolactone, while active treatment increased DLCO due to an increase of DM (DLCO: 18.3 $\pm$ 3.9 vs. 19.9 $\pm$ 5.5 mL/min/mmHg; DM: 28.1 $\pm$ 7.7 vs. 33.3 $\pm$ 8.6 mL/min/mmHg) and peak oxygen consumption (peak VO_2 16.8 $\pm$ 1.9 vs.18.6 $\pm$ 2.2 mL/min/kg). Increments of DLCO and peak VO_2 were linearly related ($R = 0.849$, $P < 0.001$).

Conclusion These data show a positive effect of spironolactone on gas diffusion and exercise capacity suggesting a novel mechanism by which anti-aldosteronic drugs improve HF clinical condition and prognosis.

Introduction

Aldosterone plasma level is increased in chronic heart failure (HF),[1–3] and it has several properties which are likely to be detrimental in HF.[4,5] Moreover, anti-aldosteronic drug treatment induces improvement in HF status and prognosis.[6,7] Aldosterone has been related to extracellular matrix turnover increase,[8,9] which is associated with cardiac, kidney and, possibly, lung fibrosis.[2,5,8,10–13] It has been proposed that drug-induced aldosterone inhibition causes a reduction of cardiac remodelling, which is one of the extra renal mechanisms of anti-aldosteronic drugs suggested as the possible cause of HF improvement.[8,11,14–17] The inhibition of aldosterone-induced extracellular matrix turnover increase is likely to be ubiquitous in the body and not limited to the heart. However, little, if any, attention has been devoted to the effect of aldosterone and anti-aldosteronic treatment on the lung in HF patients. Indeed there is experimental evidence that the lung epithelium is a physiological target tissue for aldosterone,[18–21] and that spironolactone might ameliorate pulmonary fibrosis.[13]

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The alveolar–capillary membrane undergoes chronic changes in HF,[22] which are associated with an increase in its fibrotic content.[23,24] Notably, lung diffusion abnormalities are frequently observed in HF patients,[25] are greater the more severe the disease is,[26,27] and are related to both reduction in exercise performance,[26,28] and poor prognosis.[29] As a consequence we evaluated the hypothesis that anti-aldosteronic drugs positively influence lung diffusion abnormalities in chronic HF patients.

Methods

Study population

Thirty chronic HF patients participated in the study. Patients belong to a cohort of subjects regularly followed at our HF unit. All subjects were previously evaluated by cardiopulmonary exercise testing (CPET) in our laboratory. Study inclusion criteria: New York Heart Association (NYHA) class II or III, optimized individually tailored drug treatment, stable clinical conditions for at least 2 months as confirmed by absence of relevant oedema, capability of performing a CPET, lung diffusion for carbon monoxide (DLCO) $<$80% of predicted, absence of history and/or clinical documentation of pulmonary embolism or primary valvular heart disease, pericardial disease, severe obstructive lung disease, primitive or occupational lung disease, renal failure (serum creatinine $>$2.0 mg/dL), hyperkalaemia (serum $K^+ > 5.5$ mEq/L), significant peripheral vascular disease, exercise-induced angina, ST changes, or severe arrhythmias. All patients have a recent ($<$2 months) echocardiographic evaluation.

Laboratory investigation

A blood sample was taken to measure red blood cells, haemoglobin, serum electrolytes, blood urea nitrogen, and serum creatinine as well as plasma aldosterone.

Quality of life

Quality of life was evaluated by means of the Minnesota quality of life (QOL) questionnaire.[30]

Pulmonary function and lung diffusion

All subjects were evaluated by standard pulmonary function tests, which included DLCO. Forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC) were measured according to the American Thoracic Society standard criteria,[31] using the predicted values of Quajer *et al.*[32] DLCO was measured with the single breath–constant expiratory flow technique (Sensor Medics 2200, Yorba Linda, CA, USA).[33] Diffusion subcomponents, capillary volume (Vc), and Dm were also measured applying the Roughton and Forster method.[34] For this purpose, subjects inspired gas mixtures containing 0.3% CH_4, 0.3% CO, with three different oxygen fractions equal to 20, 40, and 60%, respectively, and balanced with nitrogen.

Cardiopulmonary exercise test (CPET)

CPET was performed on a cycle ergometer (Ergo 800S Sensor Medics, Yorba Linda, CA, USA); work rate was increased in ramp pattern after 3 min of rest and 3 min of unloaded cycling. Expiratory O_2, CO_2, and ventilation (VE) were measured breath-by-breath. A 12-lead ECG was also recorded from which heart rate was obtained (V-Max, Sensor Medics, Yorba Linda, CA, USA). The test was self-ended by patients who were strongly encouraged to perform a maximal test. The rate of work rate increase during testing was decided on the basis of the patient's clinical condition and the results of previous tests. The aim was to achieve peak exercise in about 10 min. Peak exercise was considered the highest VO_2 achieved. Anaerobic threshold was measured with the V-slope analysis from the plot of VCO_2 vs. VO_2.[35] The anaerobic threshold value was confirmed by ventilatory equivalents (increase of VE/VO_2 with a constant VE/VCO_2) and end-tidal pressure (increase of end-tidal PO_2 with constant end-tidal PCO_2). The VO_2/work rate relationship was evaluated throughout the entire exercise, during the ramping period. The VE vs. VCO_2 slope was calculated as the slope of the linear relationship between VE and VCO_2 from the beginning of loaded exercise to the end of the isocapnic buffering period. Two experts independently read each test and the results were averaged.

Study design

Patients were randomly assigned to active treatment (25 mg spironolactone daily, group 1) or placebo (group 2). They were evaluated by QOL questionnaire, laboratory investigations, pulmonary function, lung diffusion, and CPET before treatment and 6 months after. Treatment was kept constant throughout the study period. Active smokers ($n = 5$) were requested not to smoke in the 2 h which preceded their arrival at the hospital. The research was open-label but research personal involved in the randomization procedure and the personnel that evaluated patients were blinded with regard to study protocol, treatment, and time course of the study. Our institutional ethics and scientific committees approved the protocol and each patient gave written informed consent to the study and to each procedure.

Table 1 Patient characteristics

	Group 1	Group 2
Age (years)	60.3 ± 9.4	57.7 ± 7.3
Sex	10 M/5 F	12 M/3 F
Weight (kg)	74 ± 14	73 ± 6
Height (cm)	169 ± 11	172 ± 6
Smoke (a/p/n)	1/9/5	4/6/5
EF (%)	40 ± 19	35 ± 11
LVDV (mL)	181 ± 29	186 ± 30
Aetiology	11P/4I	9P/6I
ACE I	14	8
β blockers	12	7
Diuretics	9	15
AT1 blockers	1	4
Digoxin	2	3
Amiodarone	3	5

Data are means ± standard deviation. EF, ejection fraction; LVDV, left ventricle volume; P, primitive cardiomyopathy; I, ischaemic cardiomyopathy.

Smoke a = actual, p = previous, n = non-smoking.

Group 1: patients receiving treatment ($n = 14$).

Group 2: patients receiving placebo ($n = 15$).

Table 2 Quality of life and pulmonary function results

	Group 1		Group 2		Changes from baseline		
	Basal	6 month	Basal	6 month	Group 1	Group 2	*P*
FEV_1 (L/min)	2.64 ± 0.69	2.58 ± 0.72	2.66 ± 0.54	2.68 ± 0.50	0.01 ± 0.23	0.03 ± 0.32	NS
FEV_1 %	84 ± 11	86 ± 11	87 ± 13	88 ± 12	3 ± 8	1 ± 9	NS
FVC (L)	3.60 ± 0.77	3.74 ± 0.74	3.55 ± 0.62	3.60 ± 0.59	0.06 ± 0.29	0.08 ± 0.67	NS
FVC %	99 ± 12	105 ± 10	95 ± 14	97 ± 12	1 ± 8	1 ± 4	NS
DLCO(mL/min/mmHg)	18.2 ± 3.8	19.9 ± 5.5	18.9 ± 3.2	19.1 ± 4.2	1.7 ± 1.3	0.7 ± 1.4	0.044
DLCO (% pred)	68.1 ± 9.4	78.5 ± 15.0	68.0 ± 7.6	69.2 ± 10.8	10.1 ± 7.6	1.5 ± 9.5	0.049
DM (mL/min/mmHg)	28.1 ± 7.4	33.3 ± 8.6	27.2 ± 6.5	27.2 ± 8,3	5.3 ± 4.1	0.2 ± 6.2	0.035
Vc (mL)	91 ± 39	75 ± 32	109 ± 51	105 ± 41	−16 ± 35	−5 ± 55	NS
Minnesota QOLq	27 ± 16	27 ± 15	26 ± 16	27 ± 17	1 ± 9	2 ± 12	NS

QOLq, quality of life questionnaire; NS, not significant.

Table 3 Renal function

	Group 1		Group 2		Changes from baseline		
	Basal	6 month	Basal	6 month	Group 1	Group 2	*P*
BUN (mg/dL)	45 ± 15	50 ± 19	45 ± 15	46 ± 16	7 ± 13	1 ± 17	NS
Creatinaemia (mg/dL)	1.18 ± 0.3	1.17 ± 0.3	1.05 ± 0.2	1.08 ± 0.3	0 ± 0.22	0.03 ± 0.30	NS
Serum K^+ (mEq/L)	4.5 ± 0.3	4.8 ± 0.4	4.5 ± 0.2	4.6 ± 0.4	0.31 ± 0.39	0.12 ± 0.34	NS
Aldosterone plasma level (pg/mL)	80 ± 36	145 ± 85	85 ± 30	90 ± 35	65 ± 57	5 ± 7	0.002

BUN, blood urea nitrogen.

Statistical analysis

Data reported are mean ± SEM. The sample size was calculated assuming an increment of peak VO_2 = 3.0 mL/min/kg in the treatment group vs. an increment of zero in the placebo group with a sigma (standard deviation = 2.5 mL/min/kg), a two-sided test, a value for alpha = 0.5 and a desired power = 0.90. Statistical analysis was performed by means of the unpaired Student's *t*-test (two-sided). Differences between groups were assessed comparing changes from baseline. A *P*-value <0.05 was considered as significant.

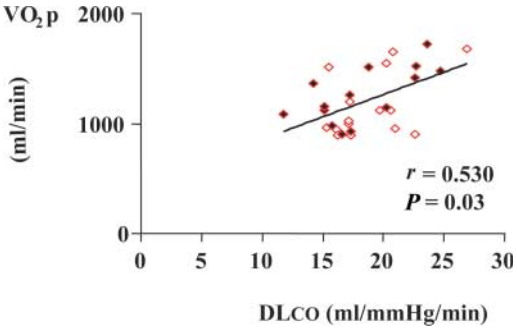

Figure 1. Oxygen consumption at peak exercise (VO_2p) vs. lung diffusion for carbon monoxide (DLCO) in the entire study population (groups 1 and 2) at baseline evaluation.

Results

Fifteen subjects received the placebo treatment and 15 were assigned to the active treatment group. Patient characteristics of both groups are reported in *Table 1*. All group 2 patients completed the 6 months follow-up while one patient of the active treatment group (group 1) abandoned the protocol because of gynaecomasty. We used the intention to treat analysis. Therefore data of the subject who abandoned the protocol are reported in the mean of group 1 data at baseline. QOL score and standard pulmonary function tests were not affected by treatment (*Table* 2). Active treatment increased DLCO due to an increase in DM while Vc was slightly reduced (*Table 2*). DLCO and DM changes from baseline with treatment were 1.7 ± 1.3 vs. 0.7 ± 1.4 mL/min/mmHg (*P* = 0.044) and 5.3 ± 4.1 vs. 0.2 ± 6.2 mL/min/mmHg in group 1 and 2, respectively (*P* = 0.035). Spironolactone treatment did not affect the kidney function while it significantly increased aldosterone plasma levels (*Table 3*). DLCO was significantly correlated with exercise capacity; *Figure 1* reports the correlation between peak VO_2 and DLCO in both groups at the pre-treatment evaluation. Active treatment increases exercise capacity. Changes from baseline with treatment of peak VO_2 was 1.8 ± 1.9 vs. 0.1 ± 1.7 mL/min/kg in groups 1 and 2, respectively (*P* = 0.01). CPET parameters in both groups are reported in *Table 4*; anaerobic threshold was reached in all tests. The

Table 4 Cardiopulmonary exercise test results

	Group 1		Group 2		Changes from baseline		
	Basal	6 month	Basal	6 month	Group 1	Group 2	*P*
VO_2p (mL/min/kg)	16.8 ± 1.8	18.6 ± 2.2	15.7 ± 3.3	15.8 ± 2.9	1.8 ± 1.9	0.1 ± 1.7	0.008
VO_2 at (mL/min/kg)	12.4 ± 2.0	12.9 ± 1.5	10.1 ± 2.2	10.1 ± 1.7	0.5 ± 1.5	−0.0 ± 2.7	NS
V_E/VCO_2	29 ± 4	30 ± 4	31 ± 8	32 ± 5	1 ± 3	2 ± 3	NS
VO_2/work (mL/min/watt)	9.3 ± 0.7	9.9 ± 0.8	8.6 ± 1.2	8.8 ± 1.1	0.6 ± 1.3	0.1 ± 0.9	NS
Watt	97 ± 22	115 ± 39	97 ± 22	99 ± 21	17 ± 20	1 ± 10	0.039
HR (beat/min)	118 ± 22	127 ± 24	137 ± 25	131 ± 24	9 ± 19	−6 ± 31	NS

VO_2p, peak oxygen consumption; at, anaerobic threshold; HR, heart rate.

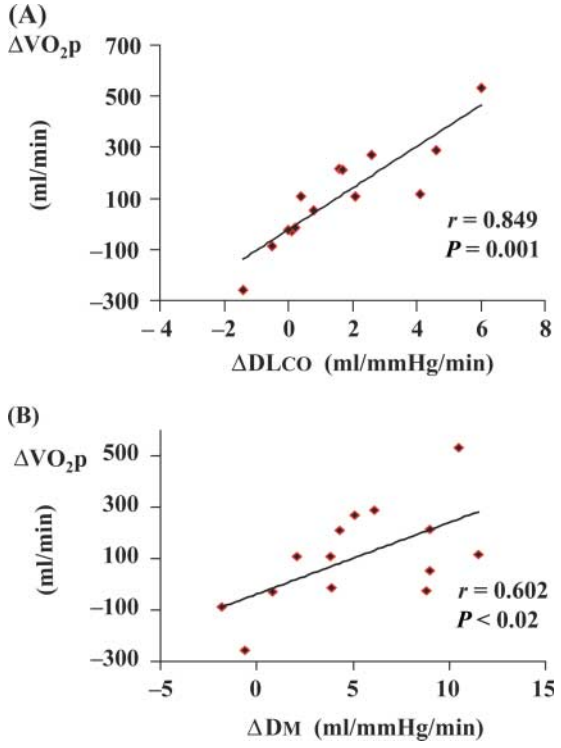

Figure 2 (*A*) Increments (6 month–baseline evaluation) of oxygen consumption at peak exercise (ΔVO_2p) vs. increments of lung diffusion for carbon monoxide (ΔDL_{CO}) in group 1. (*B*). Increments (6-month–baseline evaluation) of oxygen consumption at peak exercise (ΔVO_2p) vs. increments of membrane diffusion (ΔD_M) in group 1.

increase in DL_{CO} and D_M with active treatment was related to the increase in peak VO_2 (*Figure 2A* and *B*). No such correlations were found in the placebo group.

Discussion

The current study shows that spironolactone improves gas diffusion through the lungs and exercise capacity in stable chronic HF patients with impaired DL_{CO}. Both increments are related to each other.

It is well appreciated that spironolactone improves clinical condition and prognosis of chronic HF patients.[6,8] Data on exercise capacity are less clear. A recent paper by Cicoira *et al.*[16] showed some increase in peak VO_2 only in subjects treated with spironolactone doses >25 mg/day. The reason for this exercise capacity increase might be related to a more complete modulation of neurohumoral activation when spironolactone is added to standard HF treatment.[4,8,9,36] It has been proposed that the spironolactone-induced modulation of neurohumoral activation exerts its effect on the heart[9,11,14] or on the peripheral vasculature.[37] No data are available about pulmonary function of patients treated by anti-aldosteronic drugs.

Lung diffusion impairment is observed in HF particularly if D_M is selectively evaluated.[25–29] Both DL_{CO} and D_M are related to HF severity and prognosis.[29] Even if HF patients do not desaturate during exercise, the physiological meaning of the correlation between exercise capacity and DL_{CO} impairment is relevant.[38] Indeed in HF patients, but not in normals, haemoglobin O_2 saturation is linearly related to DL_{CO} both at rest and at peak exercise and the peak exercise alveolar–arterial O_2 difference is greater the lower the DL_{CO} is both in normoxic and hypoxic conditions.[38] Furthermore, DL_{CO} has been suggested as one of the targets of chronic HF therapy able to influence exercise capacity.[39,40] However, DL_{CO} changes are not simply a marker of exercise capacity improvement with treatment. Indeed, heart transplant,[24,41,42] ultrafiltration,[23] and AT1 blockers,[43] which are among the most effective HF treatments, do not improve DL_{CO} whilst they do improve exercise capacity.

Lung diffusion is frequently impaired in HF patients.[25–29] However, we selected our study population evaluating only chronic HF patients with a low diffusing capacity across the alveolar–capillary membrane. We did so because we believed that in HF the alveolar–capillary membrane is damaged by several factors including aldosterone as suggested by studies in rats.[13] Accordingly, we hypothesized that spironolactone treatment could, at least in part, restore gas diffusion in humans.[13] Indeed, in chronic HF patients, other drugs such as ACE-inhibitors act to modify the alveolar–capillary membrane,[39,40] improving, in a linear fashion, DL_{CO} and exercise capacity.[39] Differently from acute HF, in which lung fluid changes are the major cause of DL_{CO} changes,[44,45] in chronic HF DL_{CO}, abnormalities are independent of lung fluid content.[23,24] In fact the pressure-induced

trauma, the increase of the sympathetic tone and renin–angiotensin aldosterone system, and the activation of the inflammatory state, all lead to proliferation of alveolar type II cells, to thickening of the alveolar–capillary interstitium, to increase in lung connective tissue, including its matrix, and to lung fibrosis.[23,26,46] There is recent evidence suggesting that several lung cells have aldosterone receptors and it has been suggested that, under physiological conditions, aldosterone is involved in active Na^+ transport across the alveolar–capillary membrane.[19,21] It is not easy to link the active role of aldosterone in maintaining the lumen of the lung fluid-free and the evidence that high levels of aldosterone are found in pulmonary fibrosis and that spironolactone reduces pulmonary fibrosis. It is possible to hypothesize that, in chronic HF, because of the increase in aldosterone and lung cells which are known to have aldosterone receptors on their surface, chronic high aldosterone levels promote interstitial fibrosis possibly through local dehydration. If this is the case, aldosterone has a role in HF similar to that of catecholamines and of the renin–angiotensin system, which shift from short-term security mechanisms to long-term participants in the vicious circle of HF.[47] In any case, independently of the physiological mechanism, because the alveolar epithelium and the endothelium are target tissues for aldosterone,[18–21] it seems reasonable to suggest that the relationship we described between DLco and exercise capacity improvement with spironolactone underlines one of the mechanisms by which spironolactone improves HF clinical condition and prognosis.

Study limitations

This study has several limitations. First, we evaluated only HF patients with low DLco and therefore our results cannot be extended to patients with normal DLco. It is possible that this patient selection is responsible for differences between results of our and previous studies,[16] which reported a peak VO_2 increase only in subjects treated with higher spironolactone doses. Secondly, no measures of serum levels of markers of matrix turnover have been done in the present study. However, serum pro-collagen type III amino-terminal peptide is either an early indicator of early lung fibrosis,[48] is associated with poor HF conditions and increase of early death risks,[8,49] and its value reduces in HF patients treated with spironolactone.[8] Therefore the relationship between DLco improvement and lung connective tissue changes in spironalactone-treated HF patients is attractive but remains speculative. Thirdly, the spironolactone effects in HF are potentially ubiquitous and we limited our evaluation to the lungs. Therefore the lungs should be considered as only one of the possible sites of action of spironolactone in HF treatment.

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