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Lung function with carvedilol and bisoprolol in chronic heart failure: Is β selectivity relevant?

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Abstract

Background: Carvedilol is a β-blocker with similar affinity for β_1- and β_2 receptors, while bisoprolol has higher β_1 affinity. The respiratory system is characterized by β_2-receptor prevalence. Airway β receptors regulate bronchial tone and alveolar β receptors regulate alveolar fluid re-absorption which influences gas diffusion.
Aims: To compare the effects of carvedilol and bisoprolol on lung function in patients with chronic heart failure (CHF).
Methods and results: We performed a double-blind, cross-over study in 53 CHF patients. After 2 months of full dose treatment with either carvedilol or bisoprolol, we assessed lung function by salbutamol challenge, carbon monoxide lung diffusion (DLCO), including membrane conductance (DM), and gas exchange during exercise. FEV_1 and FVC were similar; after salbutamol FEV_1 was higher with bisoprolol ($p<0.04$). DLCO was 82±21% of predicted with carvedilol and 90±20% with bisoprolol ($p<0.01$) due to DM changes. Peak VO_2 was 17.8±4.5 mL/min/kg on bisoprolol and 17.0±4.6 on carvedilol, ($p<0.05$) with no differences in bronchial tone (same expiratory time) throughout exercise. Differences were greater in the 22 subjects with DLCO<80%.
Conclusion: Carvedilol and bisoprolol have different effects on DLCO and response to salbutamol. DLCO differences, being DM related, are due to changes in active membrane transport which is under alveolar β_2-receptor control. Peak VO_2 was slightly higher with bisoprolol particularly in CHF patients with reduced DLCO.

Keywords: Exercise; Heart failure; Bisoprolol; Carvedilol; Lung diffusion

1. Introduction

Carvedilol and bisoprolol are among the most frequently used β-blocking agents in chronic heart failure (CHF) [1–4]. The two drugs have different pharmacological characteristics, carvedilol has similar affinity for both β_1 and β_2 receptors, whereas bisoprolol has selective affinity (120-fold) for β_1 vs. β_2 receptors [5]. The respiratory system is characterized by a significant predominance of β_2 receptors, both in the airways and in the alveoli [6,7]. The role of airway β receptors in regulating bronchoconstrictor tone is well-known. However, more than 90% of β receptors in the human lungs are located in the alveoli [7,8], where they regulate fluid re-absorption from the alveolar surface [7], and thereby influence gas exchange efficacy [9,10]. In view of their different β-receptor affinities, it is likely that carvedilol and bisoprolol will have different effects on pulmonary mechanical function and gas diffusion. This is particularly important in CHF, where lung function impairment, both at rest and during exercise, is well known [11–13]. Indeed, in

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CHF, a restrictive syndrome [11,13], reduction of lung diffusion [11,12,14], bronchial hyper-responsiveness to bronchoconstrictor agents [15], as well as exercise induced hyperventilation [13] and expiratory flow limitation [16,17] have all been described. The present study was undertaken to measure lung function during chronic CHF treatment with carvedilol and bisoprolol. Lung function was evaluated by means of a standard pulmonary function test, both with and without salbutamol challenge, lung diffusion, including lung diffusion subcomponents, membrane diffusion and capillary volume and ventilation behaviour during effort.

2. Methods

2.1. Study population

Patients were recruited from a cohort of consecutive CHF subjects regularly followed at our heart failure unit. Study inclusion criteria were: CHF in NYHA class II–III, stable clinical conditions for at least 2 months, capable of perorming a maximal or near-maximal cardiopulmonary exercise test (CPET), previous experience with CPET in our laboratory; and absence of history and/or clinical documentation of pulmonary embolism, primary valvular heart disease, pericardial disease, severe obstructive lung disease, significant peripheral vascular disease, severe anaemia (haemoglobin <11 g/dL), exercise-induced angina, ST-segment changes or severe arrhythmias. The study conforms with the principles outlined in the Declaration of Helsinki and was approved by the local Ethics Committee. All subjects provided written informed consent to participate in the study.

2.2. Quality of life

Quality of life was evaluated by means of the Minnesota Living With Heart Failure Questionnaire [18].

2.3. Echocardiography

Left ventricular volume and ejection fraction were measured in the left lateral decubitus position (Sonos 5500, Andover, MA). Left ventricular volume was derived from the conventional apical 2- and 4-chamber images and the left ventricle ejection fraction was calculated using biplane Simpson's technique. Mitral insufficiency was graded by visual inspection, on a scale of 0 to 4. Pulmonary systolic pressure was estimated by Doppler analysis of the tricuspid leak with right atrial pressure estimation [19].

2.4. Standard pulmonary tests

Standard pulmonary tests were performed according to the American Thoracic Society criteria [20]. Normal predicted values for forced expiratory volume in 1 s (FEV_1) and vital capacity (VC) were those reported by Quajer et al. [21]. Tests were done before and after salbutamol challenge.

2.5. Lung diffusion

Lung diffusion was measured as lung diffusion for carbon monoxide (DLCO). DLCO was obtained in the standard sitting position with the single breath–constant expiratory flow technique (Sensor Medics 2200, Yorba Linda, CA) [22]. Diffusion subcomponents, DM and capillary volume, were also measured by applying the Roughton and Forster method [23]. For this purpose, subjects inhaled gas mixtures containing 0.3% CH_4 and 0.3% CO, with three different oxygen fractions equal to 20, 40 and 60%, respectively, and balanced with nitrogen. Alveolar volume was measured by CH_4 decay slope during single breath constant expiratory flow measurements [24].

2.6. CPETs

CPETs were done on a cyclo-ergometer (Ergo 800S Sensor Medics, Yorba Linda, CA), using a personalized ramp protocol aimed at achieving peak exercise in 10 min with breath by breath expiratory gases and ventilation analysis (V-Max, Sensor Medics, Yorba Linda, CA) [25]. The test was self-ended by the patients; however, all patients declared that they had performed what they felt to be maximal effort. Anaerobic threshold was measured with the V-slope analysis from the plot of VCO_2 vs. VO_2 on equal scales [26]. The anaerobic threshold value was confirmed by ventilatory equivalents and end-tidal pressures of CO_2 and O_2. The VO_2/work rate relationship was evaluated throughout the entire exercise; the ventilation ($\dot{V}_E$)/VCO_2 slope was calculated as the slope of the linear relationship between $\dot{V}_E$ and VCO_2 from 1 min after the beginning of loaded exercise to the end of the isocapnic buffering period. Two experts read each test independently.

Table 1
Patient characteristics

Number of patients	53
Mean age (years)	63±10
Sex	
Male	48
Female	5
NYHA	
Class II	21
Class III	32
Heart failure aetiology	
Ischaemic cardiomyopathy	22
Dilated cardiomyopathy	31
Cardiac rhythm	
Sinus rhythm	43
Atrial fibrillation	10
Therapy	
diuretics	41
ACE inhibitors	44
AT blockers	8
Digitalis	3
Amiodarone	14
Aldosterone antagonists	30
Antiplatelets/anticoagulants	40

Table shows number of patients unless otherwise indicated.

Table 2
Pulmonary function data in 53 CHF patients during carvedilol and bisoprolol treatment

	Carvedilol	Bisoprolol	*p*
Vital capacity (L)	3.69±0.89	3.75±0.94	NS
Vital capacity post-salb (L)	3.83±0.93	3.86±0.89	NS
FEV_1 (L)	2.72±0.76	2.71±0.73	NS
FEV_1 (L) post-salb (L)	2.71±0.83	2.83±0.73	0.03

CHF=Chronic heart failure; FEV_1=forced expiratory volume at 1 s; salb=salbutamol challenge.

2.7. Study design

The study was a double blind, cross-over design. Both drugs were administered b.i.d. (bis in die). Dose equivalence was 1 (bisoprolol) to 5 (carvedilol) [5] and tablets were 1.25 mg for bisoprolol and 6.25 mg for carvedilol. Patients were randomly assigned to bisoprolol or carvedilol as first treatment. All patients had previously been treated with either carvedilol or bisoprolol; the starting dose used in the study was equivalent to 50% of the dose previously used [5]. For example, if a patient had previously been treated with carvedilol 12.5 mg b.i.d., he could start the study with either carvedilol 6.25 mg b.i.d., or bisoprolol 1.25 mg b.i.d. Thereafter, doses were up-titrated every 2 weeks in order to reach the maximal tolerated dose. The maximal tolerated dose was considered to be the highest dose during which hypotension (systolic blood pressure <90 mm Hg), severe bradycardia (heart rate <44 beat/min during awake rest) or symptoms related to hypotension such as dizziness and fatigue were not observed and/or reported by patients. Once reached, the maximal tolerated dose was maintained for 2 months. On completion of the two month maintenance phase, patients were crossed-over to the other research drug, starting again with a dose equivalent to 50% of that of the previous drug. The effects of bisoprolol and carvedilol on lung function were evaluated at the end of each study period. All patients underwent a standard pulmonary function test including salbutamol challenge, lung diffusion inclusive of subcomponents, CPET as well as a standard 2D echo-Doppler evaluation.

2.8. Statistical analysis

Data reported are mean±SD. Peak exercise and anaerobic threshold VO_2 measurements are means over 20 s. Differences were analyzed by repeated measurements ANCOVA, adjusting for the timing in the cross-over design. Correlations were analyzed by linear regression analysis. A sample size of 60 patients was calculated in order to assess statistically significant differences between carvedilol and bisoprolol as regards FEV_1 and/or DLCO with a two-tailed alpha value of 0.025, a power of 90%, an expected difference between groups >10% with SD of 20% and a predicted drop-out rate of 10%. A p value <0.05 was considered as statistically significant for study parameters other than FEV_1 and DLCO.

3. Results

Sixty CHF patients in a stable clinical condition, who fulfilled the inclusion criteria, were enrolled. Seven patients were lost during the follow-up period, as follows: three revoked their consent to participate in the study, two did not show adequate compliance to therapy, and two were unable to perform pulmonary function tests. Therefore, 53 CHF patients were included in the study. CHF treatment (Table 1) was kept constant throughout the trial.

The mean dose of carvedilol was 27.1±10.0 mg/day and bisoprolol was 4.8±1.8 mg/day. Minnesota Living With Heart Failure Questionnaire scores were 26±20 for carvedilol and for bisoprolol 24±20 (p=NS). Echocardiographic measurements were similar for both treatments. Left ventricular systolic volume was 124±54 and 124±55 mL and left ventricle diastolic volume was 196±70 and 196±67 mL, for carvedilol and bisoprolol, respectively. Left ventricular

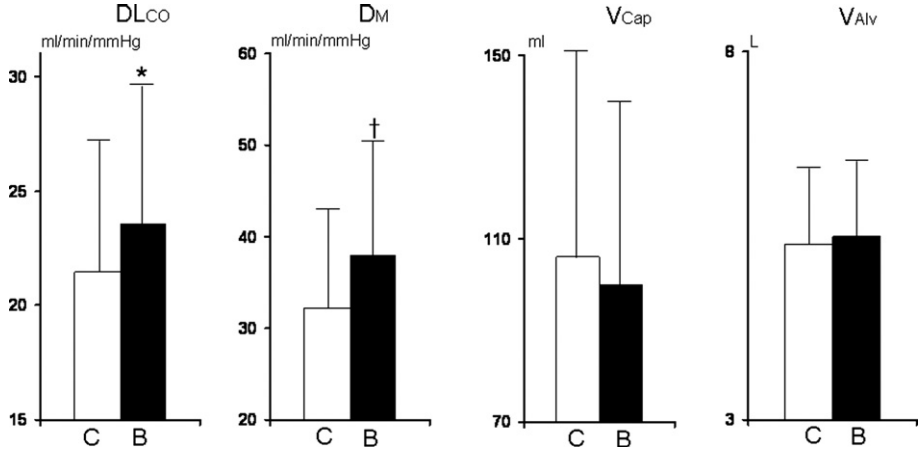

Fig. 1. From left to right: lung diffusion for carbon monoxide (DLCO), membrane conductance (DM), capillary volume (VCap) and alveolar volume (VAlv) during chronic treatment with carvedilol (C) and bisoprolol (B). *=p<0.01 vs. carvedilol; †=p<0.02 vs. carvedilol.

Table 3
Cardiopulmonary exercise test data in 53 CHF patients during carvedilol and bisoprolol treatment

	Carvedilol	Bisoprolol	*p*
Exercise tolerance (min)	9.15±1.39	9.70±1.84	0.002
Peak $\dot{V}O_2$ (mL/min)	1339±417	1400±406	0.05
Peak $\dot{V}O_2$ (mL/min/kg)	17.0±4.6	17.8±4.5	0.04
Peak work-load (W)	105±34	111±36	0.0005
Peak heart rate (b/min)	120±26	119±3.1	NS
Peak O_2p (mL/b)	11.3±3.2	11.9±3.1	NS
$\dot{V}_E/\dot{V}CO_2$ slope	30.6±5.3	30.6±5.1	NS
$\dot{V}O_2$/work slope	9.4±1.5	9.5±1.5	NS

$\dot{V}O_2$=Oxygen consumption; O_2p=oxygen pulse ($\dot{V}O_2$/heart rate); $\dot{V}_E/\dot{V}CO_2$=ventilation/carbon dioxide slope; b=beat.

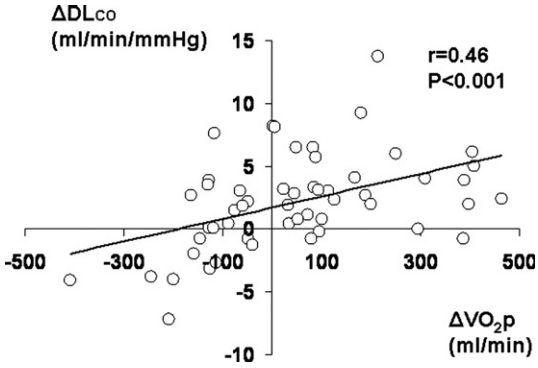

Fig. 2. Correlation between changes in lung diffusion (ΔDLCO) vs. changes in peak VO_2 (ΔVO_2p) between bisoprolol and carvedilol treatment.

ejection fraction was 37±8% and 38±9%, and mitral insufficiency was 1.3±0.9 and 1.4±0.8, respectively. It was possible to estimate systolic pulmonary pressure in 41 patients; values of 30±10 mm Hg and 30±9 mm Hg were reported for carvedilol and bisoprolol, respectively.

FEV_1 was 91±18% of predicted and 91±19% of predicted (NS) and VC was 94±16% of predicted and 96±19% of predicted (NS), for carvedilol and bisoprolol, respectively. Absolute values of pulmonary function data before and after salbutamol challenge are reported in Table 2. The FEV_1 response to salbutamol was greater with bisoprolol. Results remained similar if data from patients with FEV_1 or VC<80% of predicted were considered separately. DLCO was 82±21% of predicted and 90±20% of predicted with carvedilol and bisoprolol, respectively ($p<0.01$). Absolute values for DLCO, DLCO subcomponents and alveolar volume are reported in Fig. 1. The higher DLCO value with bisoprolol was due to an improvement in DM. Twenty-two subjects had a DLCO value <80% of predicted with either carvedilol (20 cases) or bisoprolol (17 cases). In these subjects, DLCO was 15.9±3.4 mL/min/mm Hg (63±14%) and 17.7±3.1 (72±12%) ($p<0.02$ for both absolute values and %) with carvedilol and bisoprolol, respectively.

The mean cardiopulmonary exercise ramp protocol was 11.4±2.8 W/min. Results are reported in Table 3. The effort intensity during both tests was comparable, with a similar respiratory exchange ratio (Table 3). Data showed a higher exercise performance with bisoprolol. At rest, on the cycloergometer, heart rate was 70±15 and 67±13 b/min (p=NS) for carvedilol and bisoprolol, respectively. There was no significant difference in data at anaerobic threshold (VO_2=11.3±3.1 mL/min/kg and 11.9±3.7 mL/min/kg; heart rate 97±22 b/min and 92±18 b/min, for carvedilol and bisoprolol, respectively). To assess any possible difference in exercise induced bronchodilation, ventilatory data during exercise were analyzed (Table 4). No differences were identified by our analysis. Changes in peak VO_2 between carvedilol and bisoprolol treatment were linearly related to changes in DLCO ($R=0.46$, $p<0.001$) (Fig. 2). Considering subjects with DLCO<80% predicted, peak VO_2 was 15.1±4.4 mL/min/kg and 16.7±5.8 mL/min/kg ($p<0.01$) with carvedilol and bisoprolol, respectively. Also in these 22 patients with low DLCO, changes in peak VO_2 were related to changes in DLCO ($R=0.456$, $p<0.05$).

As assessed by repeated measurements ANCOVA, no effect of the treatment sequence was observed for any of the study parameters.

4. Discussion

This is the first human study dedicated to understanding the different effects of a β_1 and a β_1–β_2 blocking agent on lung

Table 4
Ventilation, tidal volume, respiratory rate and expiratory time during exercise

	Rest [a]	2 min [a]	4 min [a]	6 min [a]	8 min [b]	Peak
$\dot{V}_E$ C (L/min)	11.1±2.6	17.2±3.9	22.9±5.0	32.5±6.8	44.1±9.8	55.0±15.7
$\dot{V}_E$ B (L/min)	10.8±2.8	17.7±4.9	23.3±5.4	32.2±7.8	43.7±11.5	56.4±14.2
Tidal volume C (L)	0.70±0.28	0.90±0.34	1.11±0.41	1.34±0.35	1.59±0.56	1.70±0.56
Tidal volume B (L)	0.68±0.27	0.91±0.31	1.13±0.36	1.30±0.37	1.57±0.43	1.73±0.51
Resp. rate C (b/m)	17±5	20±5	22±5	25±6	29±7	33±7
Resp. rate B (b/m)	17±4	21±6	22±5	26±7	28±6	33±6
Te/Ttot C	0.59±0.09	0.58±0.05	0.56±0.04	0.54±0.03	0.53±0.09	0.53±0.03
Te/Ttot B	0.59±0.06	0.58±0.05	0.57±0.05	0.55±0.03	0.53±0.09	0.53±0.03

C=Carvedilol; B=bisoprolol; $\dot{V}_E$=ventilation; Resp=respiratory; Te=expiratory time; Ttot=breath time.
[a] n=53.
[b] n=47.

function in CHF patients. Results show that chronic treatment with carvedilol (β_1–β_2 blocker) and bisoprolol (β_1 blocker) has different effects on two aspects of lung function at rest: the response to bronchodilator stimulation and lung diffusion. The difference in response to bronchodilator stimulation did not significantly affect the ventilatory pattern during exercise, but might be a safety issue in case of worsening of pulmonary congestion and the need for acute β-stimulating therapy. The difference between β-blockers on lung diffusion, being selectively related to membrane conductance, is likely due to the changes in active membrane transport which is under β_2-receptor control. During bisoprolol treatment, exercise capacity was slightly but significantly higher; however, this is unlikely to be of clinical relevance. Exercise performance differences between carvedilol and bisoprolol became more relevant if only patients with impaired DLCO were considered.

Both drugs were up-titrated to what is believed to be the maximal tolerated dose and both reached the same clinical level of β-receptor blockade. Indeed, a 1 to 5 dose relationship between bisoprolol and carvedilol is well known [5]. Furthermore, cardiac function, evaluated by echocardiography, was not different during carvedilol and bisoprolol treatments, nor was heart rate at rest or peak exercise. Similarly, the $\dot{V}_E/VCO_2$ slope, an index of ventilatory regulation positively influenced by β-blocking therapy [27], was similar with both drugs. Finally, the doses of both drugs reached in the present study are in the range reported in other clinical studies aimed at CHF treatment with maximal tolerated β-blocker doses [1–3,5]. All these observations suggest a similar degree of β-blockade.

Standard pulmonary function tests were generally normal, a few patients showed, a mild restrictive disease as is usually reported in CHF [11,13]. No difference between carvedilol and bisoprolol was observed. However, the response to inhaled salbutamol, the classic test for bronchodilation, evidenced a superior response in Bisoprolol treated patients. This is important in the case of a need for acute bronchodilation, as during asthma or recrudescence of COPD.

During exercise, expiratory flow limitation occurs in CHF patients, this limits exercise performance [16,17]. It is possible to hypothesize that the different response to salbutamol inhalation has an equivalent in the second part of the exercise, when catecholamine spill-over increases. Indeed, in normal subjects, there is an active bronchodilation during exercise [16,28] and immediately after exercise the maximal flow/volume loop is larger [17]. In the present study, we did not perform a maximal flow/volume manoeuvre during exercise (see study limitations). We limited our analysis to the expiratory time changes during exercise, and observed a similar expiratory time at all levels of exercise with carvedilol and bisoprolol (Table 4), suggesting that major differences in bronchial tone during exercise are absent.

Pulmonary oedema clearance is impaired in animal models of hydrostatic pulmonary oedema and acute lung injury [29,30]. DLCO is reduced by alveolar oedema [31]. It has been known for many years that injection of propranolol reduces DLCO in experimental animals [32]. However, only recently has it been proved that epithelial β_2-receptor signals are important for the regulation of alveolar active Na^+ transport when the lung deals with excessive fluids [33]. There is quite a bit of evidence to support this theory: a) alveolar clearance of fluid is reduced by β_2-receptor loss [33], b) catecholamines stimulate alveolar fluid clearance via activation of β receptors in human [34] and animal lungs [35,36], c) ability to clear instilled fluid is significantly impaired in β_1 and β_1–β_2 knockout mice [33], d) β stimulating agents prevent pulmonary oedema at high altitude [36] and e) β stimulating agents improve acute lung injury [7].

Lung diffusion depends on DM and capillary volume. Capillary volume is the amount of blood which participates in gas exchange. DM is the specific membrane conductance. DLCO and DM are related to alveolar volume, but alveolar volume was constant during both carvedilol and bisoprolol treatment. We have previously shown that, by acting on active ion transport at the alveolar-capillary membrane level, it is possible to directly interfere with gas diffusion, even in the absence of a haemodynamic effect. Indeed, ACE-inhibitors improve DLCO, but this effect is counteracted by aspirin [37]; while glucose infusion, though not saline infusion, improves alveolar-capillary conductance [38].

We have recently reported that carvedilol, when compared to placebo, reduces DLCO at sea level, reduces arterial pO_2 at rest and during submaximal exercise in normoxic and hypoxic conditions, and reduces exercise capacity at a simulated altitude [39]. We were not able to ascribe these findings to the blockade of alveolar β receptors, because several other causes, specifically carvedilol induced changes in cardiac function and chemoreflex responses, might have been advocated as the cause of these results. In the present study, both drugs were up-titrated to what is believed to be the maximal tolerated dose, so that differences in DLCO and DM are likely the consequence of blockade of β_2 receptors on the epithelial layer of the alveoli. Indeed, particularly in CHF patients, lung fluid homeostasis is a delicate balance between force, which drives fluids into the air space, and the physiological mechanisms which remove fluids from the alveolar surface which includes vectorial transepithelial sodium transport which is under β_2-receptor control [7,40]. The present is the first demonstration, in CHF patients, of an active role for alveolar β receptors, not only in preventing pulmonary oedema [36] but also in regulating alveolar fluid balance. It is not known, however, if the higher level of DLCO and DM observed with bisoprolol implies higher protection against pulmonary oedema [41].

It should be noted that a low DLCO, and specifically a low DM [12], are associated with an unfavourable prognosis in patients with CHF. Bisoprolol increases DLCO when compared to carvedilol in all subjects studied, but particularly in patients with a low DLCO, in other words, in patients with the worst DLCO-related prognosis. It is unknown, however, whether a change in DLCO implies a change in prognosis, and no data are available for a comparison between carvedilol and bisoprolol, in terms of prognosis.

Exercise capacity was significantly higher with bisoprolol when compared to carvedilol. The difference however was quantitatively small and likely clinically mute. Accordingly, the quality of life score was unaffected by the type of β-blocker used. However, peak VO_2 differences were clinically more relevant, on the average of 10%, particularly in subjects with low DLCO. Peak VO_2 increase with bisoprolol was related to DLCO increase, both in the entire population and in patients with DLCO <80% predicted. However, a correlation does not imply a cause–effect relationship. Indeed, other reasons may account for the peak VO_2 differences between bisoprolol and carvedilol, which we observed. In fact, cardiac contractility and chronotropy under exercise is correlated with β-receptor density [42] and bisoprolol, but not carvedilol, leads to an upregulation of down-regulated β_1 receptors. Hence, cardiac contractility reserve under conditions of enhanced sympathetic activity such as exercise, should be larger on bisoprolol treatment and this could explain the higher peak VO_2 we observed with bisoprolol.

This research has a few relevant limitations which should be addressed. First, we have no data on normal subjects. Second, we have not studied CHF patients without β-blockers. This was due to the fact that the majority of CHF patients in our cohort were already on β-blocker therapy, and it was considered unethical to withdraw β-blockers for reasons of research. Third, we have no information about the acute effect of both drugs. Indeed, to achieve a β-blocking effect in heart failure patients, the drug dose needs to be slowly and progressively up-titrated. Fourth, expiratory function during exercise is better characterized by performing a maximal flow/volume manoeuvre than by analyzing, as we did, expiratory time. So we cannot exclude some differences in expiratory flow limitation. However, we decided not to perform maximal flow/volume curves during exercise, because that would have significantly influenced VO_2 and VCO_2 measurements. Fifth, carvedilol also has an alpha-receptor blocking action. At present, there are major doubts about the function and expression of alpha receptors in the lung tissue [43]. However, alpha-blockers should, if anything, have a bronchodilating action which would have improved the respiratory response to the drug. Finally, although there was a higher peak VO_2 with bisoprolol, this does not mean that bisoprolol is superior to carvedilol in CHF, as this is only one aspect of the overall effect of β-blocker therapy. In fact, we did not measure any hard end-points and current published data suggest, if anything, a superiority of carvedilol over the β_1 selective β-blocker metoprolol [44].

Although our study was not designed to investigate differences in clinical benefit between carvedilol and bisoprolol, our findings may implicate that bisoprolol could be preferred to carvedilol, as a first line therapy, in patients presenting with a low DLCO.

In conclusion, in terms of DLCO, response to salbutamol challenge and exercise capacity, this study shows a superior effect of bisoprolol over carvedilol in CHF patients. DLCO and exercise capacity differences are more relevant in patients with a low DLCO.

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