β-Blockers and Inspiratory Pulmonary Function in Chronic Heart Failure

KLAUS K.A. WITTE, MB, MRCP, AND ANDREW L. CLARK, MA, MD, MRCP

Hull, England

ABSTRACT

Background: Chronic heart failure (CHF) patients complain of breathlessness and fatigue. Respiratory muscle function is impaired in CHF patients and may contribute to their symptoms. β-blockers cause fatigue but have become part of the standard management of CHF. We explored the relation between respiratory muscle power in CHF and the effects of long-term β-blockade.

Methods and Results: A total of 52 CHF patients and 25 control subjects underwent echocardiography, peak exercise testing with metabolic gas exchange analysis, and measurement of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), peak inspiratory flow (PIF), and forced inspiratory volume in 1 second (FIV_1). Of the patients, 35 started β-blocker therapy and were tested again at 1 year. Patients had lower peak oxygen consumption (pVO_2) (19.3 [4.5] versus 37.3 [8.4] mL/kg/min, $P < .0001$), exercise time (414 [134] versus 817 [193] seconds, $P < .0001$), and anaerobic threshold (13.8 [3.8] versus 27.2 [8.2] mL/kg/min, $P < .0001$). Patients also had a steeper relationship between ventilation (V_E) and carbon dioxide (CO_2) (V_E/VCO_2) (40.0 [6.8] versus 26.4 [2.0], $P < .0001$); lower FEV_1, FVC, and FIV_1 (89 [15] versus 111 [24]% expected, $P < .0001$, 80 [20] versus 94 [21]% expected, $P < .001$ and 2.5 [1.6] versus 3.0 (0.9) L, $P < .02$); and there was a correlation between pVo_2 and FIV_1 ($r = 0.24$, $P < .05$) for the patients. The slope relating symptoms of breathlessness (Borg score) to ventilation (Borg/V_E slope) also correlated with FIV_1 ($r = 0.36$, $P < .02$). β-blocker therapy improved echocardiographic variables, but not pVO_2. There was no change in PIF or FIV_1. There was a significant reduction in FEV_1 after β-blocker treatment ($P < .01$).

Conclusion: Inspiratory flows are impaired in patients with chronic heart failure and correlate with the degree of functional impairment. This may be due to a combination of respiratory muscle weakness and reduced lung compliance. The reduction in inspiratory capacity is not influenced by long-term β-blockade.

Key Words: Chronic heart failure, breathlessness, inspiration.

Patients with chronic heart failure (CHF) complain of exercise intolerance, usually from breathlessness and fatigue.[1] Incremental exercise testing with metabolic gas exchange measurements used to derive peak oxygen consumption (pVO_2) allows an objective assessment of symptoms and exercise capacity.[2] The breathlessness might be related to impaired pulmonary function, which is common in CHF patients when measured by forced spirometry[3,4] and correlates with exercise tolerance.[5] Contributing to these pulmonary abnormalities is a combination of increased airways resistance, reduced lung compliance,[6] and respiratory muscle weakness.[7]

In some reports, respiratory muscle strength measured by maximal inspiratory pressure measurements is reduced in CHF patients and predicts mortality[8,9] and total exercise capacity.[10] However, other reports have suggested that inspiratory pressures measured during maximal sniffs and phrenic nerve stimulation are only slightly reduced, suggesting that respiratory muscle strength is preserved.[11] There might be reduced endurance of the respiratory muscles,[12–14] and the reduced stamina in the context of increased respiratory muscle loading might contribute to breathlessness.[15,16] Specific respiratory muscle training reduced breathlessness scores during submaximal exercise and increased pVo_2 in some studies[17] but not others.[18,19]

β-receptor antagonists improve mortality and morbidity and reduce symptoms of breathlessness,[20] but their effect on exercise tolerance in patients with CHF is unclear with most studies, but not all,[21,22] showing no benefit.[23,24] Even topical (β-blockers can, however, worsen spirometry in patients with no evidence of chronic pulmonary disease.[25] The most common side effect of β-blocker therapy is fatigue. One study

From the Castle Hill Hospital, Cottingham, Hull, England.

Address for reprints: Dr K. Witte, Academic Cardiology, Castle Hill Hospital, Castle Road, Cottingham, Hull HU16 5JQ, England.

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Table 1. Subject Characteristics

	Patients (n = 52)	Controls (n = 25)	*P* value
Age (y)	69 (7.8)	67 (9.0)	.16
Height (cm)	171 (7)	175 (7)	<.05
Weight (kg)	79.3 (13.9)	80.7 (10.1)	.65
Drugs			
Frusemide*	65 (23)	0	
β-blockers (n)	10	0	
ACEi/AIIA (n)	52	0	
Spironolactone (n)	15	0	
New York Heart Association (n)			
I	0		
II	31		
III	18		
IV	3		
LVEF (%)	33.6 (5.3)	61.3 (9.4)	<.0001
LVEDD (cm)	6.5 (0.8)	5.1 (0.6)	<.0001
Peak V_{O_2} (mL/kg/min)	19.3 (4.5)	37.3 (8.4)	<.0001
V_E/V_{CO_2} slope	40.0 (6.8)	26.4 (2.0)	<.0001
AT (mL/kg/min)	13.8 (3.8)	27.2 (8.2)	<.0001
ET (s)	414 (134)	817 (193)	<.0001
RER	1.05 (0.06)	1.05 (0.06)	.87
Peak V_E (L/min)	64.5 (13.1)	90.2 (21.2)	<.0001
Peak V_T (L)	1.7 (0.4)	2.6 (0.6)	<.0001
Peak frequency (/min)	37.6 (6.6)	35.4 (5.9)	.16
Borg/V_E slope	0.17 (0.06)	0.13 (0.09)	<.05

Values are means (SD).

*The mean daily does at enrollment of frusemide is given.

ACEi, angiotensinconverting enzyme inhibitor; AIIA, angiotensin II inhibitor; LVEF, ejection fraction; LVEDD, left ventricular end diastolic dimension form M-mode echocardiography; Peak V_{O_2}, peak oxygen consumption; V_E/V_{CO_2} slope, slope relating ventilation to carbon dioxide production; AT, anaerobic threshold; ET, exercise time; RER, respiratory exchange ratio (V_{CO_2}/V_{O_2}).

has suggested that normal subjects who develop fatigue with β-blockers demonstrate reduced inspiratory flows while taking them.[26] Inspiratory flows were not altered in those that did not get fatigue. The only other study examining inspiratory strength and β-blocker therapy suggests that propranolol increases muscle strength in patients treated for thyrotoxicosis.[27] No study has examined the effect of β-blocker therapy on the function on the inspiratory muscles in patients with CHF.

The aim of this study was to examine inspiratory function in a group of patients with CHF, and to establish whether there is a detrimental effect on respiratory muscle strength with long-term use of β-receptor antagonists.

Table 2. Spirometry and Inspiratory Flow Results

	Patients (n = 52)	Controls (n = 25)	*P* value
FEV_1 (% predicted)	89 (15)	111 (24)	<.0001
FVC (% predicted)	80 (20)	94 (21)	<.001
PEFR (L/min)	5.8 (1.6)	8.2 (2.4)	<.0001
FIV_1 (L)	2.5 (1.6)	3.0 (0.9)	<.02
PIF (L/min)	3.5 (1.4)	3.8 (1.6)	.41

Values are means (SD).

FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; PEFR, peak expiratory flow rate; FIV_1, forced inspiratory volume in the first second; PIF, peak inspiratory flow rate.

Table 3. Correlations Between Spirometry and Peak Oxygen Consumption

	Correlation (*r*-value)	*P* value
FEV_1	0.66	<.0001
FVC	0.49	<.0001
PEFR	0.52	<.0001
FIV_1	0.45	<.0001
PIF	0.14	.23

Values are means (SD).

Abbreviations as for Table 2.

Methods

We investigated 52 consecutive patients with chronic heart failure and 25 controls. The controls were age-matched individuals chosen at random from the lists of local general practitioners. The study was approved by the local ethics committee.

CHF was defined as the presence of symptoms of fatigue or breathlessness on exertion and a left ventricular ejection fraction on echocardiography of less than 40% with no other cause of breathlessness apparent. The condition had to be of at least 3 months' duration with no recent exacerbation or change in medication. Patients with evidence of symptomatic chest disease, neurologic conditions, or inducible ischemia were excluded. We also excluded patients and controls with a forced expiratory volume in 1 second (FEV_1) less than 75% of predicted. None of the controls was on regular medication and all underwent echocardiography to exclude left ventricular dysfunction.

Each subject underwent symptom-limited treadmill-based maximal exercise testing using a Bruce protocol modified by the addition of a "stage 0" at onset consisting of 3 minutes of exercise at 1.61 km/h (1 mile/h) with a 5% gradient. Participants were encouraged to exercise to exhaustion. During the tests patients wore a tightly fitting face mask to which was connected a capnograph and a sample tube enabling online ventilation and metabolic gas exchange measurements (Jaeger Oxycon Delta System, Huchberg, Germany). A respiratory exchange ratio (RER), the ratio between carbon dioxide output and oxygen uptake (Vco_2/Vo_2), greater than 1 was taken to suggest a near-maximal effort. At the end of each stage and at peak exercise subjects were asked to indicate their score for dyspnea or fatigue on a scale from 0 (no symptoms) to 10 (maximal symptoms) using a standardized scoring system (Borg score).[28] We related symptoms to ventilation by plotting the Borg score against ventilation (V_E) and calculated the slope of this relationship for each test (Borg/V_E slope).[29] The anaerobic threshold (AT) was calculated using the V-slope method.[30]

Spirometry (FEV_1, forced vital capacity [FVC], and peak expiratory flow rate [PEFR]) was performed before the exercise test. Inspiratory flows (forced inspiratory volume [FIV_1] and peak inspiratory flow [PIF]) were measured after each forced expiration by encouraging the subject to breathe in as rapidly as possible aiming to fill the lungs with a single breath. The best of 3 attempts was recorded for each individual.

Patients not yet on a β-blocker were started on β-blocker therapy in accordance with local guidelines. The β-blockers were uptitrated following recognized trial protocols[31] with visits every 2 weeks until target or maximally tolerated doses were achieved. The patients were seen at regular intervals for the subsequent 12 months and invited back for repeated assessment after 1 year of β-blocker therapy.