CARDIOVASCULAR MEDICINE

The effects of α and β blockade on ventilatory responses to exercise in chronic heart failure

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Objective: To assess the influence of acute α and β blockade on ventilation and symptoms of breathlessness during exercise in patients with chronic heart failure and in controls.
Methods: 11 patients with chronic heart failure and 11 control subjects underwent repeated exercise testing with metabolic gas exchange after random, double blind administration of either an α blocker and placebo, a β blocker and a placebo, both an α blocker and a β blocker, or double placebo.
Results: Patients had a lower peak oxygen consumption (mean (SD) 20.7 (4.9) *v* 37.6 (9.6) ml/kg/min, $p < 0.0001$) and a steeper slope relating ventilation to carbon dioxide production ($\dot{V}E/\dot{V}CO_2$ slope) (26.5 (4.1) v 37.1 (8.2), $p = 0.0011$), than controls. Blood pressure was lower following α and β blockade ($p < 0.05$) and the gradients of the slopes relating heart rate to oxygen consumption following the β blocker were reduced ($p < 0.05$). Exercise time and peak ventilatory variables following β or α blockers were unchanged. Ventilation was reduced during submaximal exercise following the active medications. Combined α and β blockade produced the greatest difference ($p < 0.005$), but the α and β blockers alone also reduced ventilation ($p < 0.05$). There was no difference in perceived exertion during exercise with any of the treatments.
Conclusion: Acute sympathetic inhibition can reduce submaximal ventilation during exercise in patients with heart failure and control subjects, suggesting that autonomic nervous system activation has an important role in the abnormal ventilatory response to exercise in chronic heart failure.

Patients with chronic heart failure complain of exercise intolerance, usually because of breathlessness and fatigue.[1] This can be objectively assessed as a reduction in peak oxygen consumption ($P\dot{V}O_2$) during incremental exercise testing with metabolic gas exchange analysis.[2] Patients also have an increased ventilatory response to exercise as shown by an increase in the slope relating ventilation to carbon dioxide production ($\dot{V}E/\dot{V}CO_2$ slope).[3 4] The $\dot{V}E/\dot{V}CO_2$ slope is abnormal throughout exercise[5] and correlates inversely with $P\dot{V}O_2$, so that the greater the ventilatory response, the lower the exercise capacity.[3 4]

The cause of this abnormal ventilatory response is not clearly understood. Lung function is abnormal in patients with chronic heart failure,[6 7] and we have previously shown that patients' exercise capacity is partly limited by a reduced maximal tidal volume, leading to a greater dependence on frequency early during exercise.[8] Skeletal muscle is also involved in ventilatory control. Skeletal muscle contains receptors, termed ergoreceptors, that stimulate ventilation in response to work.[9] These receptors are overactive in heart failure and are linked to the increased sympathetic activity.[10]

A further influence on ventilation during exercise may be through central chemoreceptors.[11] Arterial blood gas tensions are normal in patients with chronic heart failure during exercise,[12 13] but the reflexes associated with these chemoreceptors are overactive in patients.[14]

Chronic heart failure is a state of sympathetic overactivity,[15] and it may be through the abnormal sympathetic nervous system that these factors exert an influence upon ventilatory control during exercise. β Blockade in chronic heart failure improves echocardiographic variables of cardiac function, patients' symptoms, and their prognosis,[16 17] but no consistent improvement in maximal[18] or submaximal[19 20] exercise capacity has been seen.

Exogenously infused catecholamines increase ventilation in control subjects.[21–23] Yohimbine, which increases catecholamine release, increases ventilation during exercise in normal subjects.[24] The aim of the present study was to assess the influence that short term α and β blockade has on the ventilatory response to exercise and symptoms of breathlessness in patients with chronic heart failure compared with a group of control subjects.

METHODS

We enrolled 11 patients with chronic heart failure caused by ischaemic heart disease and 11 control subjects into the study. Each subject gave informed, written consent before involvement in the study, which was approved by the local ethics committee. Chronic heart failure was defined as the presence of symptoms of fatigue or breathlessness on exertion and a left ventricular ejection fraction on echocardiography of < 35%. The condition had to be of at least three months' duration with no recent exacerbation. We excluded patients with neurological conditions or inducible ischaemia upon exercise and those already taking either α or β antagonists. The controls were individuals of a similar age chosen at random from the patient lists of local general practitioners. None was taking regular medication and all underwent echocardiography to exclude left ventricular dysfunction. People in both groups were excluded if there was any history of pulmonary disease or if their forced expiratory volume in one second (FEV_1) was < 80% of predicted.

Each subject underwent a familiarisation symptom limited exercise test. We used the Bruce treadmill protocol modified by the addition of a stage 0 at onset consisting of three minutes of exercise at 1.61 km/h (1 mile/h) with a 5% gradient. During the tests patients wore a tightly fitting facemask to which was connected a capnograph and a sample tube enabling online

Abbreviations: $P\dot{V}O_2$, peak oxygen consumption; RER, respiratory exchange ratio; $\dot{V}CO_2$, carbon dioxide production; VE, minute ventilation

Table 1 Subject characteristics

	Patients (n=11)	Controls (n=11)	p Value
Age (years)	68 (6.1)	67 (9.0)	0.67
Height (cm)	174 (5.5)	177 (8.5)	0.22
Weight (kg)	80.6 (15.9)	83.4 (8.8)	0.62
LVEDD (cm)	6.9 (0.7)	5.0 (0.7)	<0.0001
LVEF (%)	31.8 (2.9)	56.7 (10.4)	<0.0001
Drugs			
Furosemide*	83.4 (53.4)		
ACEi/AIIA (n)	23		
Spironolactone (n)	5		
New York Heart Association functional class (n)			
I	0		
II	4		
III	7		
IV	0		
$P\dot{V}O_2$ (ml/kg/min)	20.7 (4.9)	37.6 (9.6)	<0.0001
Exercise time (s)	471 (226)	855 (225)	0.0007
RER	1.06 (0.06)	1.08 (0.08)	0.50
HR/O_2 slope	4.25 (1.4)	2.92 (0.7)	0.01
AT	15.5 (4.8)	27.0 (7.4)	0.0003
$VE/\dot{V}CO_2$ slope	37.1 (8.2)	26.5 (4.1)	0.0011
VE peak (l/min)	64.5 (13.5)	97.4 (21.3)	0.0003
Borg/VE slope	0.28 (0.39)	0.12 (0.05)	0.017

Values are means (SD).
*Mean (SD) daily dose of furosemide (frusemide).
ACEi, angiotensin converting enzyme inhibitor; AIIA, angiotensin II inhibitor; AT, anaerobic threshold; HR, heart rate; LVEDD, left ventricular end diastolic dimension form M mode echocardiography; LVEF, left ventricular ejection fraction; $P\dot{V}O_2$, peak oxygen consumption; RER, respiratory exchange ratio ($\dot{V}CO_2/\dot{V}O_2$); VE, minute ventilation.

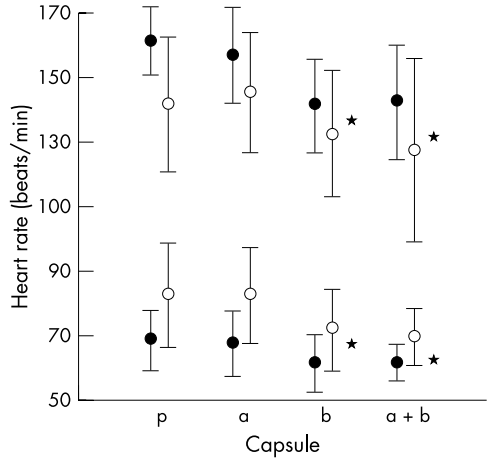

Figure 1 The effect of treatments on heart rate at rest (open circles) and at peak exercise (solid circles). *p < 0.05. a, α blocker; b, β blocker; a+b, α and β blocker; p, double placebo.

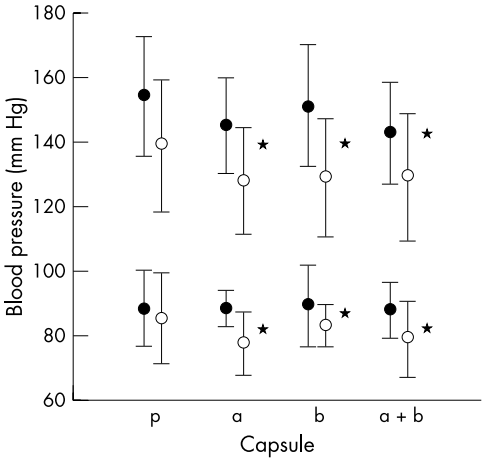

Figure 2 Effect of treatments on systolic and diastolic blood pressure at rest (open circles) and peak exercise (solid circles). *p < 0.05. a, α blocker; b, β blocker; a+b, α and β blocker; p, double placebo.

measurement of ventilation and metabolic gas exchange (Oxycon Delta system, Jaeger, Hoechberg, Germany). A respiratory exchange ratio (RER) ($\dot{V}CO_2/\dot{V}O_2$) > 1 was taken to suggest a maximal effort. The subjects were asked to score their symptoms of breathlessness or fatigue between 0–10 (0 being no symptoms and 10 being maximal) on a standard scale of perceived exertion[25] at the end of each stage during the test.

At four subsequent visits, the exercise tests were repeated 30 minutes after the administration of either an α blocker (doxazocin 2 mg) and a placebo, a β blocker (metoprolol 25 mg) and a placebo, both (metoprolol 25 mg and doxazocin 2 mg), or double placebo in a randomised double blind fashion.

Results are reported as mean (SD). The anaerobic threshold was calculated by the $\dot{V}CO_2/\dot{V}O_2$ slope method.[26] We plotted the relation of Borg score against expired minute ventilation (VE) (Borg/VE slope) and compared the slopes acquired by simple regression. To compare submaximal responses, we used data from the last stage completed by all subjects (stage 0). We used unpaired Student's *t* test for between group comparisons of the baseline data and analysis of variance with Fisher's PLSD correction for comparisons between treatments. A probability value of $p < 0.05$ was taken to be significant.

RESULTS

Table 1 shows the baseline variables for the patients and control subjects. Patients had a shorter exercise time and a lower $P\dot{V}O_2$. The relation between VE and $\dot{V}CO_2$ was steeper in patients than in controls. There was a significantly steeper slope relating expired volume (VE) to symptoms (Borg score) in patients, so that for a given VE, patients were more breathless.

There was no difference in metabolic gas analysis variables between the familiarisation test and the test conducted with double placebo.

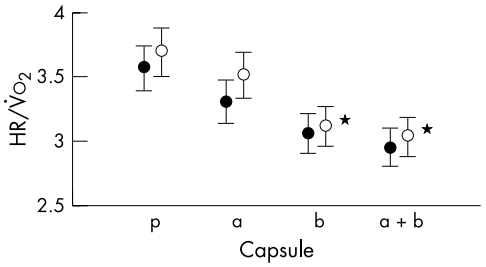

Figure 3 Effect of treatments on the ratio of heart rate to oxygen consumption during the tests in patients (open circles) and controls (solid circles). *p < 0.05 for reductions from placebo for both patients and controls. a, α blocker; b, β blocker; a+b, α and β blocker; p, double placebo.

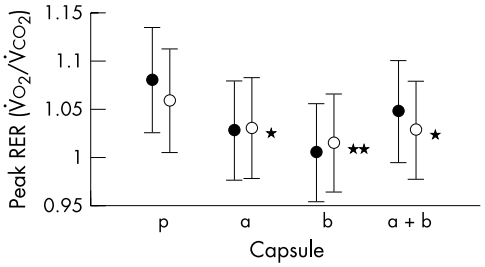

Figure 4 Effect of treatments on peak respiratory exchange ratio (RER) in patients (solid circles) and controls (solid circles). **p < 0.02; *p < 0.05 for patients and controls. a, α blocker; b, β blocker; a+b, α and β blocker; p, double placebo.

Haemodynamic variables

Figures 1 and 2 show the rest and peak heart rates and blood pressures for patients and controls. The differences in heart rate between the tests performed following β blockade and those following placebo and α blockade are significant ($p < 0.05$). The systolic blood pressure at rest and at peak exercise was significantly lower in both patients and controls for the tests following α and β blockade ($p < 0.05$). The effect of the β blocker can also be seen in fig 3 with significantly lower gradients of the slopes relating heart rate to oxygen consumption during the tests following β blocker ingestion ($p < 0.05$).

Ventilatory variables

There were no significant differences in exercise time or peak ventilatory variables following β or α blocker for either patients or controls. The $P\dot{V}O_2$, $VE/\dot{V}CO_2$ slope, and tidal volume were also not different. Table 2 displays the results for the patients and controls combined. Despite this lack of differences, patients and controls reached a significantly lower RER after the β blocker ($p < 0.02$) than after either the α blocker or placebo (fig 4). At matched submaximal workload, the RER was significantly lower after the β blocker and the combination treatments ($p < 0.05$) (fig 5).

There was also a significant reduction in VE following administration of the active medication at submaximal exercise (fig 6). The combination treatment produced the greatest difference in the patients ($p < 0.005$), but the α and β blockers alone also reduced ventilation ($p < 0.05$). None of the active treatments reduced ventilation significantly more than any other. Reductions in ventilation were also seen at higher levels of exercise, but only the effect of the combined active treatments reached significance at the second stage (stage 1) ($p < 0.05$) and this was no longer significant by the third (stage 2) ($p < 0.07$). During the early stages of exercise ventilation decreased more with all active treatments than with placebo ($p < 0.01$) in the control group compared with patients, with the greatest effect following the combination treatment ($p < 0.005$). The effect was significant to the end of the second stage ($p < 0.05$) but was not significant by the end of the third ($p = 0.28$).

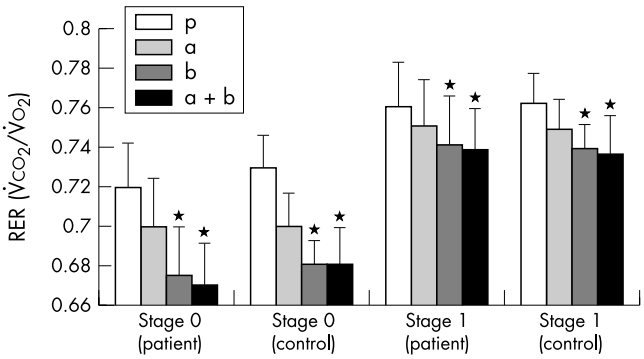

Figure 5 Effect of treatments on RER at the end of stage 0 and stage 1 in patients and controls. *p < 0.05. a, α blocker; b, β blocker; a+b, α and β blocker; p, double placebo.

Symptom scores

Overall there was no difference in the slopes relating symptoms to VE (Borg/VE). The Borg score at each stage was also not influenced by the adrenergic blockers ($p = 0.44$ for the difference between Borg score with placebo and the combination treatment tests at the end of the first stage).

DISCUSSION

The origin of the increased ventilatory response to exercise in patients with chronic heart failure remains elusive. However,

Table 2 Peak exercise variables after drug and placebo administration

Variable	Treatment				
	a	b	a+b	p	p Value
Exercise time (s)	730 (335)	692 (294)	700 (313)	712 (300)	0.97
$P\dot{V}O_2$ (ml/kg/min)	29.5 (11.1)	28.9 (10.8)	29.0 (11.6)	29.2 (11.4)	1.0
$VE/<\dot{V}CO_2$ slope	31.8 (7.7)	31.8 (7.6)	31.8 (8.1)	31.8 (8.4)	1.0
VE (l/min)	82.0 (23.1)	76.7 (20.9)	81.9 (27.7)	81.0 (24.2)	0.94
V_T (l)	2.2 (0.5)	2.2 (0.5)	2.2 (0.6)	2.2 (0.5)	0.99
Frequency (breaths/min)	37.4 (6.9)	36.0 (6.3)	36.5 (6.6)	36.5 (7.8)	0.97
RER	1.03 (0.03)	1.01 (0.08)	1.04 (0.11)	1.07 (0.07)	<0.02
HR (beats/min)	151 (19)	137 (19)	136 (26)	151 (21)	<0.05
SBP (mm Hg)	190 (35)	186 (31)	181 (37)	197 (33)	<0.05
DBP (mm Hg)	97 (26)	106 (24)	98 (26)	107 (27)	<0.05
Borg/VE slope	0.13 (0.05)	0.15 (0.05)	0.17 (0.15)	0.20 (0.28)	0.57
HR/O_2	3.4 (0.9)	3.1 (0.9)	3.0 (0.9)	3.5 (1.0)	<0.05

p Values are for analysis of variance differences between the active treatments and placebo.
a, α blocker; b, β blocker; a+b, α and β blocker; DBP, diastolic blood pressure; p, double placebo; SBP, systolic blood pressure; V_T, tidal volume.

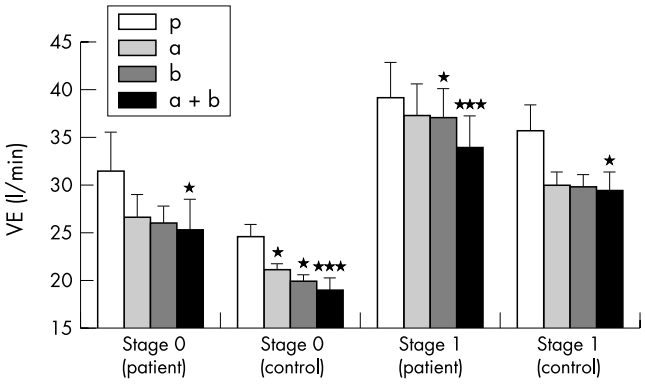

Figure 6 Effect of treatments on ventilation at the end of stage 0 and stage 1 in patients and controls. * $p < 0.05$; ***$p < 0.005$. a, α blocker; b, β blocker; a+b, α and β blocker; p, double placebo.

there is good evidence for a role of the sympathetic nervous system. Heart failure is a state of chronic sympathetic overactivity that may lead to increased sensitivity of the central chemoreceptors and hence an increased ventilatory response to hypercapnia.[11] Further receptors that can stimulate ventilation and are sensitive to sympathetic activation exist in the peripheral muscles.[9 10]

Each of these mechanisms may contribute to the pathophysiological response to exercise in patients with chronic heart failure. The common factor in the heightened sensitivity of the receptors and the increased ventilatory response is sympathetic nervous system activation.[21–23]

The potential influence of increased plasma catecholamine concentrations was shown in a group of normal subjects with the use of yohimbine. This agent prevents the negative feedback of catecholamines at the presynaptic membrane and leads to increased noradrenaline and adrenaline release, increases the ventilatory response of normal subjects, and heightens symptoms of breathlessness during steady state exercise.[24]

In the present study heart rate and blood pressure were decreased with the β and α blockers. There was also a reduction in the slope relating heart rate to oxygen consumption. The effect of the α and β receptor blockers on these haemodynamic variables implies that the delay between administration of the treatment and the tests was sufficient for the agents to be taking effect. Given that blood pressure and heart rate changes are unrelated to exercise intolerance in patients with chronic heart failure, it is unlikely that the changes in the haemodynamic variables caused the altered ventilatory response.[27 28]

Submaximal ventilation was reduced, however, with the greatest effect seen following the combination of α and β blockade. The influence of the β and α blockers on submaximal ventilation was most pronounced in the control group, and one may speculate that this reflects the activity of the agents in the presence of lower baseline catecholamine concentrations. This result supports previous findings that the sympathetic nervous system influences ventilation, both in patients with chronic heart failure and in normal subjects.[21–23] It also suggests that the increased response is not fixed and may therefore be modifiable. There was no influence on basic exercise variables such as $P\dot{V}o_2$ and $VE/\dot{V}co_2$ slope or on the ventilatory equivalent for carbon dioxide ($\dot{V}eqco_2$) by either β or α blockade.

There was no effect on the perception of breathlessness, unlike the changes noted with yohimbine. However, that study looked at normal people at submaximal exercise. It is possible that the degree of exertion required to perform a peak exercise test masked a subtle reduction in symptoms in the present study.

The influence of β and α blockade on the RER has not been described previously. The well recognised fatiguing effects of β blockade may have led subjects to perform less well in the presence of these agents at peak. However, the exercise time, $P\dot{V}o_2$, and other peak ventilatory variables were not different. The lower RER at the end of the early stages may suggest altered substrate utilisation. It is possible that after adrenergic blockade fatty acids are metabolised in preference to glucose, thereby lowering the RER.

Despite plausible explanations for the abnormalities of ventilation in heart failure, large multicentre randomised controlled trials have failed to show any benefit on exercise capacity and symptom scores from long term β blockade.[18–20] The studies suggesting improved exercise capacity in patients on long term β blockade used small study populations.[29 30] There is also no benefit on exercise capacity of adding α blockers to standard β blockers.[31]

Conclusion

The major symptom of chronic heart failure is exercise intolerance caused by breathlessness or fatigue. Despite the well documented beneficial effects of β blockade on prognosis and left ventricular ejection fraction there is no evidence of an improvement in exercise capacity. The present study, examining the effects of acute sympathetic blockade in a group of patients and control subjects, has documented reduced ventilation during the early stages of exercise in both patients and controls. This supports the concept that sympathetic activation contributes to the excessive ventilation in chronic heart failure.

Limitations

We feel that randomising the order of treatment administration and keeping the time between tests to at least one week eliminated the effects of training. The influence of performing five peak tests over a period of five weeks remains a potential but unlikely confounding variable. A possible further limitation is that of reproducibility. However, we found no difference between the familiarisation tests and those performed after double placebo suggesting good reproducibility and a lack of training effect.

We chose the doses of the α and β blockers to avoid possible side effects of hypotension and bradycardia, but it is possible that in the chronic state of sympathetic overactivity associated with heart failure, greater doses would have led to more pronounced effects. As mentioned above, the effects of yohimbine were tested at submaximal exercise in normal subjects. It is possible that the influence of the sympathetic nervous system is greatest at low to medium levels of exertion, before the respiratory and cardiovascular systems are stressed to peak, and that beneficial effects in the present study were masked by the nature of the peak tests. Indeed, any benefits at submaximal workloads would be most appropriate for patients with chronic heart failure, who rarely exercise to the levels achieved during a peak test.

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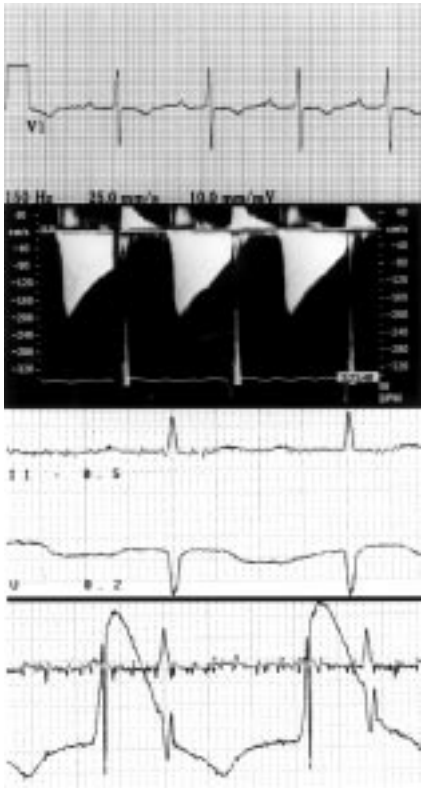
IMAGES IN CARDIOLOGY

Left atrial standstill in a patient with mitral stenosis and sinus rhythm: a risk of thrombus hidden by left and right atrial electrical dissociation

An 81 year old patient was admitted for percutaneous mitral balloon valvotomy. His ECG showed sinus rhythm with first degree atrioventricular block (top panel). However, at transthoracic and transoesophageal echocardiography (upper middle panel) the mitral Doppler signal had no A wave of augmented flow during atrial systole. Transoesophageal imaging showed the left atrium (dimension 5.3 cm) inert, while the right atrium contracted vigorously. Similar findings were seen at left and right atrial angiography. At cardiac catheterisation transmitral pressure gradient showed no "a" wave of left atrial contraction. Following successful Inoue balloon dilatation an F6 pacing electrode, attached to the chest lead of the catheter table ECG system, was passed via a Mullins Sheath to the left atrium and recordings were made from several sites on the left atrial cavity wall: no electrical activity corresponding to the p wave of the surface ECG was seen (lower middle panel—50 mm/s). When repositioned against the right atrial wall large atrial depolarisations were recorded (bottom panel).

In this patient, who had no evidence of amyloid, left atrial standstill was obscured by the right and left atrial electrical dissociation. Long term warfarin treatment was mandatory because of the risk of left atrial thrombus.



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