ESC European Society of Cardiology

European Journal of Heart Failure (2020)
doi:10.1002/ejhf.1854

RESEARCH ARTICL

Benefit of buspirone on chemoreflex and central apnoeas in heart failure: a randomized controlled crossover trial

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Received 7 April 2020; revised 14 April 2020; accepted 16 April 2020

Aims Increased chemosensitivity to carbon dioxide (CO_2) is an important trigger of central apnoeas (CA) in heart failure (HF), with negative impact on outcome. We hypothesized that buspirone, a $5HT_{1A}$ receptor agonist that inhibits serotonergic chemoreceptor neuron firing in animals, can decrease CO_2 chemosensitivity and CA in HF.

Methods and results The BREATH study was a randomized, double-blind, placebo-controlled, crossover study (EudraCT-code 2015-005383-42). Outpatients with systolic HF (left ventricular ejection fraction <50%) and moderate-severe CA [nocturnal apnoea-hypopnoea index (AHI) ≥15 events/h] were randomly assigned to either oral buspirone (15 mg thrice daily) or placebo for 1 week, with a crossover design (1 week of wash-out). The primary effectiveness endpoint was a decrease in CO_2 chemosensitivity >0.5 L/min/mmHg. The primary safety endpoint was freedom from serious adverse events. Sixteen patients (age 71.3 ± 5.8 years, all males, left ventricular ejection fraction 29.8 ± 7.8%) were enrolled. In the intention-to-treat analysis, more patients treated with buspirone (8/16, 50%) had a CO_2 chemosensitivity reduction >0.5 L/min/mmHg from baseline than those treated with placebo (1/16, 6.7%) (difference between groups 43%, 95% confidence interval 14–73%, $P = 0.016$). Buspirone compared to baseline led to a 41% reduction in CO_2 chemosensitivity ($P = 0.001$) and to a reduction in the AHI, central apnoea index and oxygen desaturation index of 42%, 79%, 77% at nighttime and 50%, 78%, 86% at daytime (all $P < 0.01$); no difference was observed after placebo administration (all $P > 0.05$). No patient reported buspirone-related serious adverse events.

Conclusions Buspirone reduces CO_2 chemosensitivity and improves CA and oxygen saturation across the 24 h in patients with HF.

Keywords Buspirone • Central apnoeas • Cheyne–Stokes respiration • Chemoreflex • Chemosensitivity • Heart failure

Introduction

Central apnoeas (CA) are observed in about 50% of patients with heart failure (HF), both during the day and at night.[1,2] Considering the epidemiological prevalence and strong contribution of CA to HF mortality,[2,3] several therapeutic approaches have been attempted: supplemental oxygen (O_2) and/or carbon dioxide (CO_2) administration,[4,5] respiratory stimulants,[6] drugs altering pH,[7] pacemakers,[8] non-invasive mechanical ventilation,[9,10] and phrenic nerve stimulation.[11] Currently, no treatment has shown a prognostic benefit in HF,[9,10] with adaptive servo-ventilation actually showing an increased risk of harm, despite being effective in reducing CA at night.[10] Some authors have hypothesized that CA may be compensatory, at least in a subset of patients with

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HF.[12] Alternatively, adaptive servo-ventilation may cause some negative effects on feedbacks/cardiac haemodynamics or cause a rebound in daytime CA, which were invariably associated with detrimental outcome in HF.[2,13]

Notably, most treatments were evaluated only at night, without targeting daytime CA or the chemoreflex, a major pathophysiological trigger of CA in HF.[14,15] Considering the prognostic significance of increased chemosensitivity[14,15] in HF, treatments that directly act on the chemoreflex could represent an effective approach, even beyond the effects on CA. The surgical removal of peripheral chemoreceptors, albeit promising in animal models of HF,[16] resulted in hypoventilation and worsening of O_2 profile in some humans, consistent with their key role as hypoxia sensors.[17]

Central chemoreceptors, which are only sensitive to hypercapnia,[18] are an alternative target. Serotonin (5-hydroxytryptamine, 5-HT) neurons play an important role in central chemoreception.[19,20] Buspirone is a 5-HT_{1A} receptor agonist long and safely used in general anxiety disorder. Some 5-HT_{1A} receptors are found as autoreceptors on 5-HT neurons, and their activation leads to inhibition of firing of 5-HT neurons. Interestingly, in a mouse model of CA induced by hypoxia/reoxygenation, intraperitoneal injection of buspirone decreased central chemosensitivity to CO_2 in a dose-dependent fashion, leading to ventilatory stability and CA disappearance.[21]

Based on this premise, we designed the BREATH study, a randomized, double-blind, placebo-controlled phase II trial with a crossover design to test the safety and efficacy of buspirone on CO_2 chemosensitivity and CA in patients with systolic HF.

Methods

From December 2016 to March 2018, stable ambulatory patients with systolic HF and CA were enrolled at the Fondazione Toscana Gabriele Monasterio (FTGM), Pisa, Italy. The study protocol conforms to the 1975 Declaration of Helsinki, was approved by the Institution's human research committee (Comitato Etico Area Vasta Nord-Ovest, Pisa, Italy) and registered at EU Clinical Trials (EudraCT code 2015-005383-42). Written informed consent was obtained from each patient.

Inclusion criteria were: age between 18 and 80 years; echocardiographic evidence of left ventricular ejection fraction (LVEF) <50% and moderate-severe CA [nocturnal apnoea-hypopnoea index (AHI) ≥ 15 events/h and >50% of apnoeas being central].

Exclusion criteria were: New York Heart Association (NYHA) class IV, acute coronary syndrome or HF, coronary artery revascularization, cardiac resynchronization therapy within 3 months before examination; severe renal dysfunction [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 by the Modification of Diet in Renal Disease equation]; liver failure; severe chronic obstructive pulmonary disease; obstructive sleep apnoeas; treatments acting on ventilation; pregnancy/no contraception in premenopausal women; alcohol/drug abuse; allergies to buspirone/drug components; myasthenia gravis; tight angle glaucoma and active neoplasia.

Randomization and masking

The galenic preparation (tablets with identical appearance) of the experimental drugs (buspirone or placebo) was performed at the Galenic Laboratory of FTGM, Massa, Italy, by a hospital pharmacist, who created a computerized randomization list (0 = placebo, 1 = buspirone) and delivered to the study staff the masked complete treatments (I and II) in sealed opaque envelopes. The randomization list remained hidden from patients and investigators (double blind) until the conclusion of the study.

Procedures

Eligible patients received, on top of optimal medical therapy, either buspirone or placebo in random order for 1 week, then underwent 1 week of wash-out before crossing over to the other treatment arm for another week. The week of treatment was chosen to achieve the drug steady-state (usually reached by day 7)[22] minimizing the overall duration of the study and thus the risk of period effect. The week of wash-out was based on the drug half-life (2–3 h up to 11 h) to avoid the risk of carryover effect.[23]

To minimize adverse reactions, the cumulative dose was titrated every 2 days from 15 mg/day (5 mg thrice daily), to 30 mg/day (10 mg thrice daily), to 45 mg/day (15 mg thrice daily) in patients with an eGFR ≥70 mL/min/1.73 m^2. For patients with an eGFR 50–69 mL/min/1.73 m^2 or 30–49 mL/min/1.73 m^2, the drug was titrated to a maximum dose of 30 mg/day or kept at 15 mg/day, respectively. To maintain masking, similar procedures related to drug titration were used for placebo.

At baseline and at the end of each week of treatment, patients underwent: 24 h cardiorespiratory monitoring for detection of CA[2,24]; evaluation of chemosensitivity to O_2 and CO_2[14] (also re-evaluated at the end of wash-out to exclude the period effect); neuro-hormonal evaluation[14]; cardiopulmonary exercise testing[14]; arterial blood gas analysis; 24 h Holter electrocardiographic recording; self-evaluation of anxiety, depression and diurnal sleepiness, by means of the Hamilton Anxiety Scale (HAM-A), the Inventory of Depressive Symptomatology (IDS), Quick Inventory of Depressive Symptomatology (QIDS) scales and the Epworth Sleepiness Scale (ESS), respectively.

The description of the 24 h cardiorespiratory monitoring and chemoreflex assessment is reported in detail in the online supplementary *Methods S1*.

Study endpoints

The pre-specified primary effectiveness endpoint was a reduction in CO_2 chemosensitivity or hypercapnic ventilatory response (HCVR) >0.5 L/min/mmHg.

Secondary effectiveness endpoints were reductions in nocturnal and diurnal AHI, central apnoea index (CAI) and oxygen desaturation index (ODI), and effects on cardiopulmonary function, neurohormones, arrhythmias, arterial blood gas analysis, anxiety, depression and diurnal sleepiness.

The primary safety endpoint was freedom from serious drug-related adverse events.

All endpoints were evaluated at 1 week after treatment administration.

Statistical analysis

Statistical analysis was performed with the SPSS 21.0 program (1989–2012, LEAD Technologies Inc., Charlotte, NC, USA). Values are presented as mean ± standard deviation (SD) or median and interquartile range (IQR) according to normal/skewed distribution.

From pilot data, considering a SD of 0.36 L/min/mmHg (repeated intra-subject measures) and >0.5 L/min/mmHg (>25% reduction from baseline) as a clinically significant (from mathematical models)[25] reduction in CO_2 chemosensitivity, recruitment of eight patients was needed to obtain 90% power with a two-sided α error rate of 0.05. To ensure robustness of our findings, we recruited 16 patients.

Considering the crossover design, we tested the period effect and the carryover effect using the Wilcoxon signed rank test.[26]

The primary effectiveness endpoint was evaluated in all patients who were randomized to either placebo or buspirone in the intention-to-treat (ITT) analysis. Patients randomized without chemoreflex data (intolerance to the test) or who withdrew from the study were imputed as treatment failures. A per-protocol (PP) analysis was also performed for the primary outcome. Finally, imputation analysis by median substitution was also performed. In order to test the primary endpoint, a two-sided McNemar's exact test was used with a type I error rate of 0.05.

The statistical analysis plan specified that each secondary endpoint would be evaluated by ITT analysis only if the primary effectiveness endpoint was significant. All patients were included in the safety analysis.

Differences from baseline between placebo and buspirone treatments were evaluated using the McNemar's test for categorical data, or the Wilcoxon signed-rank test for quantitative data [95% confidence interval (CI) by Hodges–Lehmann estimator], with a two-sided *P*-value set at 0.05. Mean differences among groups (baseline, placebo and buspirone) were evaluated through the Friedman test, with post-hoc Bonferroni correction, and a two-sided *P*-value set at 0.017.

Results

A total of 16 consecutive HF patients were enrolled (age 71.3 ± 5.8 years, all males, 50% ischaemic aetiology, LVEF 29.8 ± 7.8%, 38% in NYHA class III) and showed moderate-severe CA at nighttime, despite optimal treatment (*Figure 1*, *Table 1*). No patient withdrew from the study, two patients were intolerant to the chemoreflex test, while all other measurements were available in all patients (*Figure 1*).

Due to the crossover design, period and carryover effects were excluded before data analysis [all $P > 0.05$ for both HCVR and hypoxic ventilatory response (HVR)].

In ITT analysis, more patients treated with buspirone (8/16, 50%) had a CO_2 chemosensitivity reduction >0.5 L/min/mmHg from baseline than those treated with placebo (1/16, 6.7%) (difference between groups 43%, 95% CI 14% to 73%, $P = 0.016$; *Table 2*, *Figure 2A*). Similar findings were observed in the PP population (8/14, 57.1% vs. 1/14, 7.1%; difference between groups 50%, 95% CI 18% to 82%, $P = 0.016$) and by using imputation analysis (10/16, 63% vs. 1/16, 6.7%; difference between groups 56%, 95% CI 32% to 81%, $P = 0.004$). Buspirone decreased the HCVR by 41% and 40% compared to baseline ($P = 0.001$) and placebo ($P = 0.006$) with a difference from baseline between treatments of −0.6 (IQR −1.1 to −0.2) L/min/mmHg ($P = 0.006$; *Table 2*, *Figure 2A*).

In contrast, buspirone did not significantly affect the HVR compared to baseline and placebo [both $P > 0.017$; difference from baseline between treatments 0.0 (IQR −0.2 to 0.1) L/min/%, $P = 0.8$; *Table 2*, *Figure 2B*].

Similarly, no significant effect was observed after buspirone administration on baseline ventilation or arterial blood gas analysis parameters (all $P > 0.05$; *Table 2*), apart from a non-statistically significant trend toward an increase in the partial pressure of CO_2 ($P = 0.09$).

Buspirone was associated with a significant improvement in ventilatory stability across the 24 h with a 42% ($P = 0.001$) and 40% ($P = 0.002$) reduction in nighttime AHI [difference from baseline between treatments −12.0 (IR −16.5 to −4.3) events/h, $P = 0.002$; *Table 2*, *Figure 3A*] and a 50% ($P = 0.01$) and 36% ($P = 0.006$) reduction in daytime AHI [difference from baseline between treatments −3.5 (IQR −6.8 to −1.3) events/h, $P = 0.006$] compared to baseline and placebo (*Table 2*, *Figure 3B*). Buspirone was associated with a 79% ($P = 0.001$) and 68% ($P = 0.002$) reduction in nighttime CAI [difference from baseline between treatments −5.0 (IQR −8.0 to −0.5) events/h, $P = 0.016$; *Table 2*, *Figure 3C*] and a 78% ($P = 0.01$) and 75% ($P = 0.009$) reduction in diurnal CAI compared to baseline and placebo [difference from baseline between treatments −1.5 (IQR −5.5 to 0.0) events/h, $P = 0.01$; *Table 2*, *Figure 3D*].

These changes were accompanied by improvement in O_2 saturation after buspirone administration, as expressed by a 78% ($P = 0.004$) and 77% ($P = 0.005$) reduction in nighttime ODI [difference from baseline between treatments −8.9 (IQR −20.0 to −0.2) events/h, $P = 0.005$; *Table 2*], as well as an 86% ($P = 0.005$) and 90% ($P = 0.006$) reduction in daytime ODI compared to baseline and placebo [difference from baseline between treatments −1.9 (IQR −4.1 to −0.4) events/h, $P = 0.006$; *Table 2*]. No difference in the effect of buspirone on AHI, CAI and ODI were observed at sensitivity analysis between the whole population ($n = 16$) and the subgroup of patients with chemoreflex data available ($n = 14$) (online supplementary *Table S2*).

No statistically significant effect on neurohormonal status (apart from a slight decrease in aldosterone levels, $P = 0.04$), arrhythmic profile, or exercise performance was observed after buspirone administration (all $P > 0.05$; online supplementary *Table S1*). Buspirone had neutral effect also on anxiety (HAM-A), depression (IDS and QIDS) and daytime sleepiness (ESS) (all $P > 0.05$; online supplementary *Table S3*).

None of the patients complained of any major side effects. Only three patients with eGFR between 30 and 50 mL/min/1.73 m^2 reported mild and transient buspirone-related side effects (online supplementary *Table S3*), including lower limb tingling ($n = 1$) and dizziness ($n = 2$). One patient reported dizziness during both placebo and buspirone administration. Notably, no significant variation in troponin levels, renal and liver function was found after buspirone administration (all $P > 0.05$; online supplementary *Table S4*).

Discussion

In this single-centre, double-blind, randomized, placebo-controlled crossover trial, modulation of CO_2 chemosensitivity was documented in patients with systolic HF by using buspirone, a 5-$HT1_A$ receptor agonist. To our knowledge, this is the first proof of concept study to suggest that a pharmacological treatment might decrease central chemoreflex sensitivity in humans, showing at the same time potential beneficial effects on both nighttime and daytime apnoeas, which have, similarly to chemoreflex sensitization,[14] a prognostic role in HF[2,3,27].

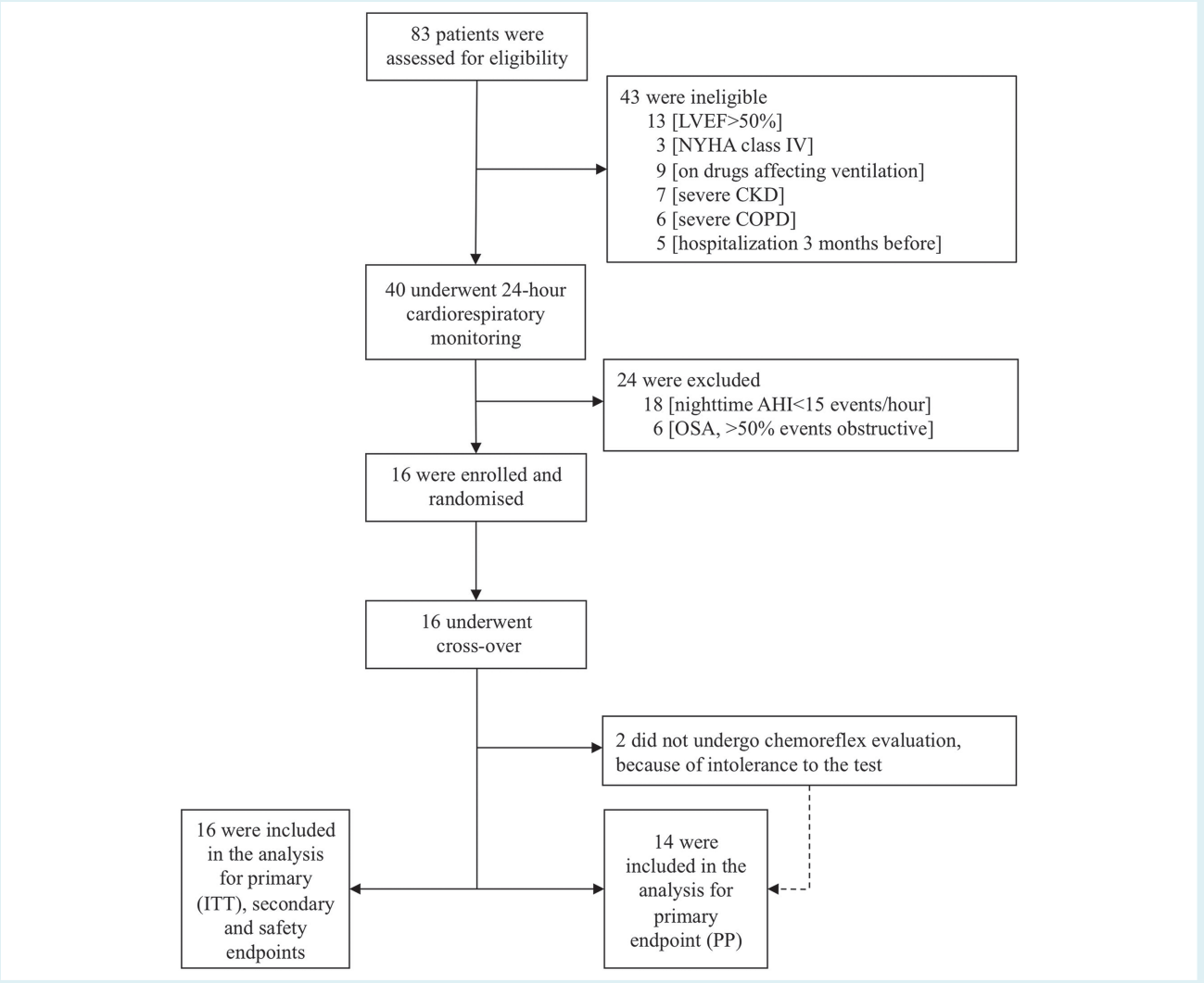

Figure 1 Trial profile. AHI, apnoea/hypopnoea index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ITT, intention to treat; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OSA, obstructive sleep apnoea; PP, per-protocol.

After one week of treatment with buspirone, CO_2 chemosensitivity was decreased by 41%, with no effect on O_2 chemosensitivity. This translated in a 24 h CA stabilization, with nighttime AHI and CAI decrease by 42% and 79% and daytime AHI and CAI by 50% and 78%, and improvement in the O_2 saturation profile, with a 77% and 86% reduction in nighttime and daytime ODI. Of note, no major buspirone-related adverse reactions did occur.

Central apnoeas can be observed in up to 60% of HF patients at night and 30% during the day.[2] Despite the well-established prognostic impact and ease of diagnosis with ambulatory devices,[2,27] no proposed treatment has ever targeted diurnal CA. Likewise, no treatment has specifically targeted the overactive chemoreflex system, a main pathophysiological trigger of CA and a prognostic determinant in HF.[1,12,13]

The surgical removal of peripheral chemoreceptors has led to promising results in animal models of HF,[14] but led to hypoventilation and need for ventilatory support in one patient in humans, given their key role in hypoxia sensing and tonic maintenance of ventilation.[15] Therefore, targeting central chemoreceptors may be a safer and similarly effective option, given their role in response to hypercapnia but not hypoxia.

Among the several groups of central chemoreceptors,[16] serotonergic neurons of the raphe system possess several characteristics that make them excellent targets for treatment: they are required for 30% to 50% of the chemoreflex response to CO_2, they are sensitive to changes in CO_2 around the ventilatory equilibrium, and their firing rate can be modulated by a number of well-characterized serotonergic medications.[18–21,28,29]

Buspirone is a 5-HT_{1A} receptor agonist used in general anxiety disorder with an excellent safety profile. It does not cause sedation, tolerance, or physical dependence. Buspirone decreases CO_2 chemosensitivity in a mouse model of hypoxia-induced apnoeas, and decreases CA.[21] Similar results were also obtained with 8-hydroxy-2-(di-n-propylamino)tetralin, another 5-HT_{1A} receptor

Table 1 Demographics and baseline clinical characteristics of patients ($n = 16$)

Age (years)	71.3 ± 5.8
Male sex (%)	100
BMI (kg/m^2)	27.4 ± 4.2
Creatinine (mg/dL)	1.3 ± 0.4
eGFR (mL/min/1.73 m^2)	63.6 ± 24.6
Ischaemic/idiopathic/other (%)	50/31/19
NYHA class I/II/III (n)	2/8/6
Blood pressure (mmHg)	120/60 ± 25.9/12.9
Heart rate (bpm)	66.5 ± 6.9
Atrial fibrillation (%)	31
LVEF (%)	29.8 ± 7.8
Diastolic dysfunction, grade 1–2/3 (%)	62/38
Mitral regurgitation, grade 0–2/3 (%)	62/38
SPAP (mmHg)	41.0 ± 18.6
TAPSE (mm)	20.4 ± 2.6
FAC (%)	39.9 ± 10.2
Norepinephrine (ng/L)	613.0 (438.5–1018.3)
Direct plasma renin (μU/mL)	104.2 (14.6–500.0)
Aldosterone (ng/L)	104.2 (67.3–131.5)
BNP (ng/L)	631.5 (269.5–1411.3)
NT-proBNP (ng/L)	2947.0 (1125.8–4491.3)
Beta-adrenergic receptor blockers (%)	94
ACE inhibitors or ARBs (%)	81
ARNI (%)	19
MRAs (%)	100
Diuretics (%)	94
Digoxin (%)	25
CRT-ICD (%)	75

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; BNP, B-type natriuretic peptide; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate (Modification of Diet in Renal Disease equation); FAC, fractional area change; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, amino terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

agonist, in rats and piglets.[30,31] Indeed, the activation of 5-HT$_{1A}$ inhibitory autoreceptors on serotonin neurons leads to inhibition of their firing, and this consequently is expected to decrease their response to hypercapnia. These data were confirmed by the current study in which buspirone was effective in decreasing CO_2 chemosensitivity and stabilizing breathing in patients with HF and CA.

Our findings were in discordance with the data of Rapoport *et al.*,[32] who found no effect on CO_2 chemosensitivity of buspirone in healthy individuals ($n = 9$, all males). Potential explanations for this discrepancy may be the use of the lower dose (10 vs. 45 mg), the shorter duration of treatment (a single dose vs. 1 week of treatment) and different effects of the drug on normal vs. overactive chemoreceptors. The dose is particularly relevant considering that the bioavailability of oral buspirone is significantly reduced by hepatic first-pass metabolism.[33] However, several active metabolites are generated including 1-(2-pyrimidinyl)-piperazine, buspirone N-oxide, and 3, 5 and 6-hydroxybuspirone, with 1-PP and 6-hydroxibuspirone showing the highest plasma concentrations in humans.[33] While 1-PP effect on 5-HT1$_A$ receptor seems trivial,[34] 6-hydroxibuspirone is likely to mediate part of the buspirone effects (similar potency/affinity to the receptor).[33]

After buspirone administration there was a trend toward a non-statistically significant reduction in plasma norepinephrine levels, that might be explained by the ability of buspirone to decrease the chemoreflex gain. Indeed, the chemoreflex also has an adrenergic output,[14,35] as documented by the increase in norepinephrine plasma levels observed after stimulating the chemoreflex with constant elevation of CO_2.[5] It is likely that higher doses/longer administration of buspirone may further decrease the sympathetic drive due to either central chemoreflex desensitization, or indirectly by decreasing CA or O_2 desaturations (thus reducing stimulation of peripheral chemoreceptors).

Administration of buspirone does not require monitoring of plasma concentrations, as opposed to theophylline,[6] and has an overall safer profile, especially on arrhythmias. Compared to acetazolamide, which reduces exercise capacity and ventilatory efficiency during cardiopulmonary stress testing,[7] buspirone shows neutral effects on exercise performance.

Moreover, buspirone is effective throughout the 24 h period,[2] with positive effects on CA not only at nighttime, but also during the daytime. Considering the prevalence/prognostic significance of daytime apnoeas[2,27] also in the upright position,[36] this may represent a benefit over previous treatments of CA such as gas delivery,[4,5] non-invasive mechanical ventilation[9,10] and phrenic nerve stimulation,[11] which are designed to work only at nighttime, for compliance reasons. Buspirone might be effective also on awake patients in freely moving conditions.

When given orally buspirone has negligible effect of the cardiovascular system even using doses (up to 10 mg/kg) much higher than those currently used for anxiety disorders, but seems to be associated with positive renal effects including increased urinary volume and electrolyte (especially sodium) excretion.[37] Furthermore, BALB/c knock-in mice with dilated cardiomyopathy presented reduced cardiac enlargement and improved systolic function after buspirone administration.[38]

Although buspirone administration may initially increase REM sleep latency by post-synaptic 5HT$_{1A}$ (less than other azapirones),[39] in the long term, the decrease of serotonin in the synaptic cleft due to the pre-synaptic action, and the positive effects on CA (associated with fragmented sleep and arousals) are likely to improve sleep quality.

Study limitations

The present study should be interpreted as a proof of concept considering the single-centre nature and the sample size (similar to previous studies based on theophylline, $n = 15$, or acetazolamide, $n = 12$),[6,7] suggesting caution when interpreting negative findings (i.e. exercise performance, neurohormonal status and side effects). The efficacy and safety of the drug should be evaluated in larger/longer multicentre trials, before considering buspirone a reasonable treatment option in patients with HF and CA. While

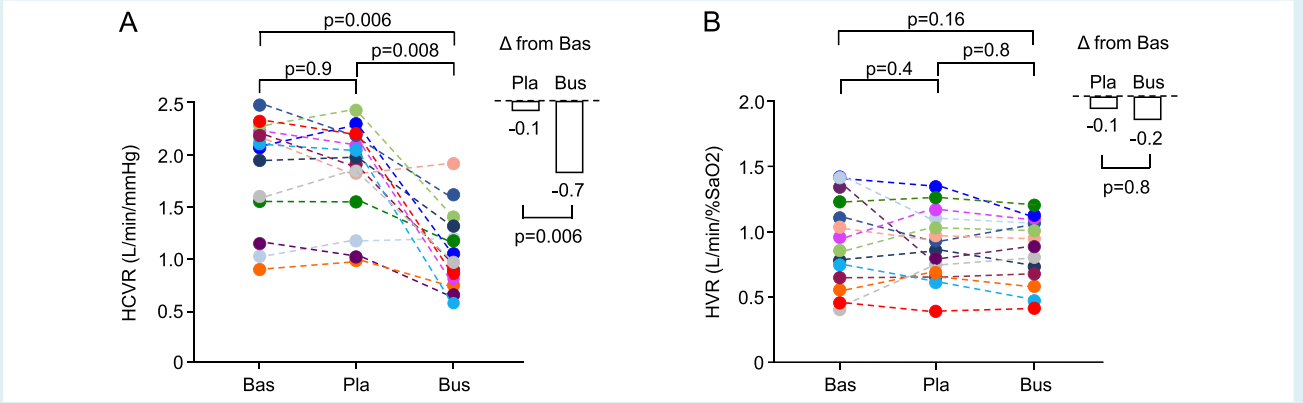

Figure 2 Effects of buspirone (Bus) on the chemoreflex. Effects of Bus on hypercapnic ventilatory response (HCVR, *A*) and hypoxic ventilatory response (HVR, *B*). Bus effectively reduced HCVR compared to baseline (Bas) and placebo (Pla), but had no effect on HVR.

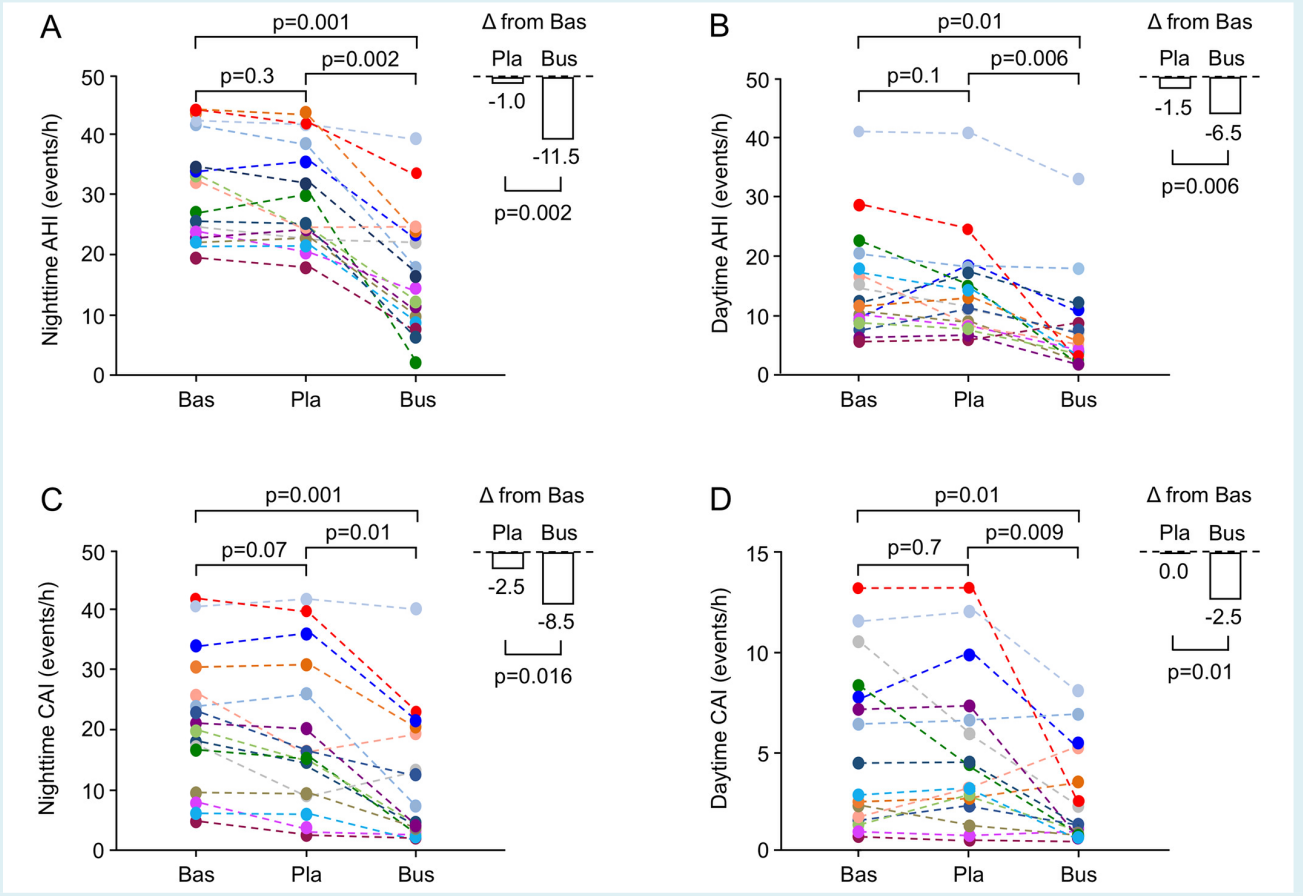

Figure 3 Effects of buspirone (Bus) on ventilatory stability. Bus decreased the apnoea-hypopnoea index (AHI, *A* and *B*) and central apnoea index (CAI, *C* and *D*) at nighttime and daytime, when compared to baseline (Bas) and placebo (Pla).

Table 2 Blood gas analysis, chemoreflex and central apnoeas following buspirone administration

	Baseline	Placebo	Change from baseline with placebo	Buspirone	Change from baseline with buspirone	Difference between treatments	*P*-value*	95% CI§
Patients with 0.5 L/min/mmHg reduction in HCVR (%; 95% CI)								
ITT	–	–	6.3 (7 to 20)	–	50.0 (23 to 78)	43.7 (19 to 68)	0.016	–
PP	–	–	7.1 (8 to 23)	–	57.1 (28 to 87)	50.0 (24 to 76)	0.016	–
Imputation analysis	–	–	6.3 (7 to 20)		63.0 (36 to 89)	56.3 (32 to 81)	0.004	–
HVR (L/min/%)	0.7 (0.4 to 1.0)	0.6 (0.3 to 0.9)	−0.1 (−0.4 to 0.2)	0.6 (0.2 to 0.9)	−0.2 (−0.3 to 0.1)	0.0 (−0.2 to 0.1)	0.8	−0.2 to 1.3
HCVR (L/min/mmHg)	2.1 (1.5 to 2.3)	2.0 (1.6 to 2.2)	−0.1 (−0.2 to 0.3)	1.2 (1.1 to 1.5)	−0.7 (−1.1 to 0.2)	−0.6 (−1.1 to −0.2)	0.006	−1.1 to −0.2
Nocturnal AHI (events/h)	28.5 (22.3 to 39.3)	27.5 (23.0 to 37.3)	−1.0 (−3.8 to 2.0)	16.5 (8.5 to 24.7)	−11.5 (−18.0 to 6.0)	−12.0 (−16.5 to −4.3)	0.002	−15.5 to −5.0
Diurnal AHI (events/h)	16.0 (6.3 to 20.0)	12.5 (6.3 to 18.8)	−1.5 (−7.3 to 0.8)	8.0 (2.3 to 11.5)	−6.5 (−10.5 to 1.5)	−3.5 (−6.8 to −1.3)	0.006	−7.0 to −1.5
24 h AHI (events/h)	18.0 (13.5 to 27.0)	17.0 (13.3 to 24.3)	−3.0 (−5.3 to 0.8)	13.0 (6.2 to 17.0)	−8.5 (−13.8 to 2.0)	−6.0 (−8.8 to −1.8)	0.002	−8.0 to −3.0
Nocturnal CAI (events/h)	19.0 (9.0 to 28.0)	12.5 (8.3 to 27.3)	−2.5 (−6.3 to 0.1)	4.0 (1.0 to 19.0)	−8.5 (−15.8 to 2.3)	−7.5 (−14.5 to 0.5)	0.016	−12.5 to −1.5
Diurnal CAI (events/h)	4.5 (1.0 to 11.8)	4.0 (1.3 to 6.0)	0.0 (−0.8 to 1.8)	1.0 (0.0 to 3.0)	−2.5 (−8.8 to 0.8)	−1.5 (−5.5 to 0.0)	0.01	−5.5 to −0.5
24 h CAI (events/h)	10.5 (6.3 to 16.8)	8.0 (6.0 to 16.3)	−2.0 (−3.0 to 0.0)	3.0 (0.3 to 9.8)	−6.0 (−9.5 to 3.0)	−5.0 (−8.0 to −0.5)	0.01	−7.0 to −2.0
Nocturnal OAI (events/h)	0.0 (0.0 to 1.0)	0.5 (1.5 to 0.0)	1.0 (0.0 to 2.0)	0.0 (0.0 to 1.0)	0.0 (0.0 to 2.0)	0.0 (−1.3 to 0.0)	0.09	−1.5 to 0.0
Diurnal OAI (events/h)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	1.0	−0.5 to 0.0
24 h OAI (events/h)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.3)	0.0 (0.0 to 1.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (−0.3 to 0.0)	0.60	−0.5 to 0.0
Maximal apnoea duration (s)	42.5 (26.0 to 52.0)	44.5 (26.5 to 70.3)	2.0 (−5.0 to 39.3)	39.5 (15.3 to 52.2)	−1.0 (−12.0 to 14.0)	−1.0 (−30.8 to 6.8)	0.4	−35.0 to 8.0
Minimal SaO_2 (%)	85.0 (73.0 to 88.0)	86.0 (73.0 to 89.0)	0.0 (−2.5 to 3.5)	89.0 (86.0 to 92.0)	0.0 (0.0 to 3.0)	1.0 (−1.3 to 3.5)	0.32	−2.0 to 4.0
Nocturnal ODI (events/h)	21.0 (10.0 to 27.7)	20.5 (8.8 to 25.5)	−0.7 (−2.0 to 1.8)	4.7 (1.0 to 11.0)	−8.1 (−20.5 to 1.0)	−8.9 (−20.0 to 0.2)	0.005	−16.5 to −3.4
Diurnal ODI (events/h)	1.4 (0.8 to 6.0)	2.0 (0.4 to 4.8)	0.2 (−0.7 to 0.7)	0.2 (0.1 to 0.7)	−1.3 (−5.3 to −0.8)	−1.9 (−4.1 to −0.4)	0.006	−5.0 to −1.0
24 h ODI (events/h)	10.0 (4.9 to 12.0)	8.0 (5.5 to 11.0)	−1.0 (−2.0 to 1.0)	3.0 (0.5 to 4.5)	−7.0 (−9.5 to −0.5)	−5.2 (−7.5 to −1.5)	0.006	−7.1 to −1.8
pH	7.42 ± 0.03	7.42 ± 0.03	0.0 ± 0.0	7.41 ± 0.04	0.0 ± 0.0	0.0 ± 0.0	0.7	0.0 to 0.0
$PaCO_2$ (mmHg)	36.1 ± 3.8	36.3 ± 3.8	0.13 ± 1.89	38.2 ± 4.1	1.0 ± 2.1	0.9 ± 2.0	0.09	0.0 to −2.0
PaO_2 (mmHg)	77.9 ± 12.3	82.2 ± 9.2	4.4 ± 13.16	81.7 ± 11.3	3.9 ± 8.8	−0.5 ± 10.3	0.8	−6.5 to 6.0
HCO_3— (mEq/L)	23.7 ± 2.0	23.7 ± 2.0	0.0 ± 1.6	23.7 ± 1.7	0.4 ± 1.6	0.4 ± 1.6	0.36	−0.7 to 1.2

Values are expressed as mean ± standard deviation for variables with normal distribution, median (interquartile range) for variables with skewed distribution.

AHI, apnoea-hypopnoea index; CAI, central apnoea index; HCVR, hypercapnic ventilatory response; HCO_3—, bicarbonate; HVR, hypoxic ventilatory response; ITT, intention-to-treat analysis; ODI, oxygen desaturation index; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; PP, per-protocol analysis; SaO_2, oxygen saturation; T90, time spent with oxygen saturation <90%.

*Two-sided from Wilcoxon signed-rank test for difference in change from baseline between placebo and buspirone administration (unless specified ITT analysis).

§95% CI for the Wilcoxon test is calculated with the Hodges–Lehmann estimator; 95% CI for the McNemar test cannot be calculated as one of the discordant values is zero.

tolerance/adaptation might occur with time, other potential beneficial effects may also be observed (sympathetic drive and sleep) considering the slower onset of the drug compared to other anxiolytic medication.

Our study population included only male patients, due to the higher prevalence of CA in men with systolic HF (80–90% in our population).[2] Therefore, its efficacy/safety should be confirmed also in women, according to gender-specific differences,[18] as well in patients with HF and preserved ejection fraction.

Conclusions

In patients with HF, oral administration of buspirone reduced the chemoreflex sensitivity to CO_2, the number of CA and hypopnoeas, and improved the O_2 saturation profile during both the day and at night. The safety profile of the drug and the pathophysiologically based mechanism of action make buspirone a reasonable treatment of CA in HF to be tested in larger phase III randomized controlled trials. We believe the results of this study will extend beyond HF, fostering research on chemoreflex modulation in other respiratory/neurological disorders, including other forms of sleep apnoea, sudden unexpected death in epilepsy and sudden infant death syndrome.[16,18,23]

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Methods S1. Supplementary methods.

Table S1. Neurohormones, Holter ECG and cardiopulmonary exercise testing following buspirone administration.

Table S2. Sensitivity analysis.

Table S3. Anxiety, depression and diurnal sleepiness after buspirone administration.

Table S4. Buspirone safety profile.

Acknowledgements

We thank the nurses (Assunta Agazio, CN and Eleonora Benelli, CN) and sleep technicians (Francesca Bramanti, MT and Giovanni Iudice, MT) of Fondazione Toscana G. Monasterio, Pisa, Italy for their technical support, as well as the members of Pharmacy of Fondazione Toscana G. Monasterio, Massa, Italy (Stefania Biagini, MSc, Giuseppa Lo Surdo, MSc, and Elisabetta Volpi, MSc) for their assistance in the preparation of placebo and randomization procedures.

Funding

G.B.R. received funding from the US NIH U01NS090414.

Conflict of interest: none declared.

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