Acetazolamide and Inhaled Carbon Dioxide Reduce Periodic Breathing During Exercise in Patients With Chronic Heart Failure

ANNA APOSTOLO, MD,[1] PIERGIUSEPPE AGOSTONI, MD, PhD,[1,2] MAURO CONTINI, MD,[1] LAURA ANTONIOLI, MD,[1] AND ERIK R. SWENSON, MD[3]

Milan, Italy; Seattle, Washington

ABSTRACT

Background: Periodic breathing (PB) during sleep and exercise in heart failure (HF) is related to respiratory acid-base status, CO_2 chemosensitivity, and temporal dynamics of CO_2 and O_2 sensing. We studied inhaled CO_2 and acetazolamide to alter these factors and reduce PB.

Methods and Results: We measured expired and arterial gases and PB amplitude and duration in 20 HF patients during exercise before and after acetazolamide given acutely (500 mg intravenously) and prolonged (24 hours, 2 g orally), and we performed overnight polysomnography. We studied CO_2 inhalation (1%−2%) during constant workload exercise. PB disappeared in 19/20 and 2/7 patients during 2% and 1% CO_2. No changes in cardiorespiratory parameters were observed after acute acetazolamide. With prolonged acetazolamide at rest: ventilation +2.04 ± 4.0 L/min ($P = .001$), tidal volume +0.11 ± 1.13 L ($P = .003$), respiratory rate +1.24 ± 4.63 breaths/min (NS), end-tidal PO_2 +4.62 ± 2.43 mm Hg ($P = .001$), and end-tidal PCO_2 −2.59 ± 9.7 mm Hg ($P < .001$). At maximum exercise: Watts −10% ($P < .02$), VO_2 −61 ± 109 mL/min ($P = .04$) and VCO_2 101 ± 151 mL/min ($P < .02$). Among 20 patients, PB disappeared in 1 and 7 subjects after acute and prolonged acetazolamide, respectively. PB was present 80% ± 26, 65% ± 28, and 43% ± 39 of exercise time before and after acute and prolonged acetazolamide, respectively. Overnight apnea/hypopnea index decreased from 30.8 ± 83.8 to 21.1 ± 16.9 ($P = .003$).

Conclusions: In HF, inhaled CO_2 and acetazolamide reduce exercise PB with additional benefits of acetazolamide on sleep PB. (*J Cardiac Fail 2014;20:278−288*)

Key Words: Oscillatory ventilation, cardiopulmonary exercise test, polysomnography.

Nocturnal and daytime periodic breathing (PB) in patients with moderate to severe chronic heart failure (HF) is not uncommon and is independently predictive of earlier mortality.[1] This is true also for PB during exercise or exercise oscillatory ventilation.[2] The genesis of PB in HF has been attributed to a variety of factors, including reduced cardiac output resulting in an increased transit time of blood from the pulmonary vasculature to the central and peripheral chemoreceptors, low lung volume, pulmonary congestion, and augmented peripheral chemoreceptor sensitivity leading to a lower eupneic (baseline) $PaCO_2$ and a narrowing of the difference between the eupneic $PaCO_2$ and the apneic (or hypoventilatory) $PaCO_2$ threshold.[3] Notably, a central hypothesis for PB genesis has also been proposed. This hypothesis is based on a derangement of the vasomotor rhythm which modulates ventilation either indirectly through blood flow modulation or directly through central irradiation to the respiratory centers.[4−6]

We have previously shown that addition of 250 mL and 500 mL of added external dead space reduced PB during exercise in HF patients. This was most evident as the nadir tidal volume (Vt) of each cycle approached the peak Vt,[7] supportive of the idea that lung volume may be a factor. Yet as a result of the added dead space, end-tidal PCO_2

From the [1]Centro Cardiologico Monzino, IRCCS, Milan, Italy; [2]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy and [3]Pulmonary and Critical Care Medicine, Veterans Administration Puget Sound Health Care System, University of Washington, Seattle, Washington.

Manuscript received October 3, 2013; revised manuscript received December 23, 2013; revised manuscript accepted January 7, 2014.

Reprint requests: Piergiuseppe Agostoni, MD, PhD, Centro Cardiologico Monzino, IRCCS, Cardiovascular Section, Dept. of Clinical Sciences and Community Health, University of Milano, via Parea, 4 (20138) Milano, Italy. Tel: +39-2-58002586; Fax: +39-02-58002398. *E-mail addresses:* piergiuseppe.agostoni@unimi.it or piergiuseppe.agostoni@ccfm.it

See page 287 for disclosure information.

1071-9164/$ - see front matter

http://dx.doi.org/10.1016/j.cardfail.2014.01.007

($PetCO_2$) rose and we could not rule out suppression of PB by an increase in the eupneic to apneic PCO_2 difference. Others have shown in HF patients that inspiration of low concentrations of CO_2 (3%) reduces PB or Cheyne-Stokes respiration by this same mechanism.[8–10] A third and independent means to possibly alter the eupneic-apneic PCO_2 difference favorably is by administration of acetazolamide, a carbonic anhydrase (CA) inhibitor that acts by several mechanisms to reduce PB during sleep at high altitude[11,12] and in those with HF.[13,14] In a small study of 12 patients with HF, Fontana et al[14] found that low-dose acetazolamide (250 mg twice a day) for 4 days did not eliminate PB during exercise in the 50% of patients who displayed the phenomenon, although it was effective in the whole group in reducing the nocturnal and diurnal apnea-hypopnea indexes.

Our aims in the present study were to measure during exercise in HF patients with an acetazolamide dose capable of altering both peripheral and central CO_2 chemosensitivity.[15] To do so, we studied the drug effect after an acute intravenous administration (500 mg) and compared it with the response following 3 oral doses over 24 hours (500 mg every 8 hours). The difference in the 2 dosing regimens was to determine whether the suppression of PB by acetazolamide is due to its effects on chemoreceptor and red cell CA inhibition (acute administration) independently from its known stimulant effect on ventilation (V_E) arising from the metabolic acidosis of renal CA inhibition that requires several hours to develop and 12–24 hours to be fully established (prolonged administration). Additionally, we sought to compare the acetazolamide effects with those of low concentrations of inhaled CO_2 (1%–2%) able to generate roughly the same small magnitude of tissue hypercapnia occurring from inhibition of red cell and vascular endothelial cell CA with acetazolamide.[12]

Materials and Methods

We studied 20 consecutive patients with HF (New York Heart Association [NYHA] functional classification II–III) and PB during exercise. These patients belong to the cohort of our HF clinic, who undergo routine follow-up which includes clinical and laboratory evaluations, echocardiography, spirometry, and cardiopulmonary exercise test (CPET). PB was defined as a cyclic fluctuation of ventilation present at rest and during exercise, with amplitude swings >30% of the mean V_E, >15% for ≥60% of incremental exercise duration.[16] The protocol was approved by our Institutional Ethics Committee (ClinTrials.gov NCT00517426), and written informed consent was obtained from each patient.

Study inclusion criteria were evidence of HF in stable clinical conditions, LVEF <40%, PB during exercise, and age 18–80 years. Study exclusion criteria were presence of unstable angina, NYHA functional class IV, recent (<6 mo) myocardial infarction, severe valvular disease, severe obstructive or restrictive lung disease (1-second forced expiratory volume or functional vital capacity <60% of predicted value), symptomatic peripheral vascular disease or orthopedic problems that could limit exercise performance, and neurologic diseases, such as dementia, stroke, or cerebrovascular disease.

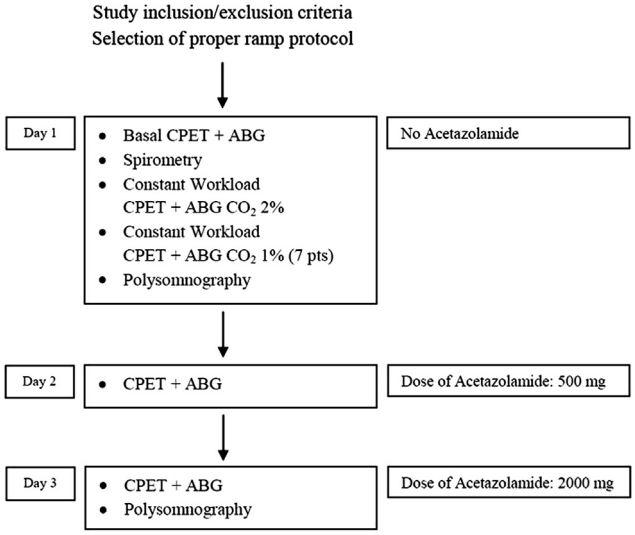

Fig. 1. Flow-chart of the tests performed. CPET, cardiopulmonary exercise test; ABG, arterial blood gas test.

To select patients for this study, we performed the following tests in patients regularly followed in our HF clinic: cardiac ultrasound evaluation to determine left ventricular volume and ejection fraction (LVEF), standard spirometry to exclude severe lung disease, and maximal ramp (5–10 W/min) symptom-limited CPET for familiarization purposes and to select patients with PB during exercise. During the CPET performed with a cycle ergometer, patients breathed through a mouthpiece connected to a mass flowmeter. We used a personalized ramp protocol aimed at achieving a maximal effort in ~10 minutes. If this was not obtained, the ramp protocol was adjusted accordingly in a 2nd test to achieve a 10-minute duration. The loaded exercise was preceded by a few minutes (>5 min) of resting ventilation measurements and by a >3-minute period of unloaded pedaling. V_E, oxygen consumption (VO_2), and carbon dioxide production (VCO_2; V-max; Sensormedics, Yorba Linda, California) were measured breath by breath. A 12-lead electrocardiogram was recorded continuously to derive heart rate and monitor for ischemic or ectopic changes. During exercise, arterial pressure was measured every 2 minutes by sphygmomanometer. All patients meeting the inclusion/exclusion criteria underwent 3 days of testing. Figure 1 is a consort diagram of the experimental protocol.

Day 1

On the 1st study day, patients performed a ramp CPET (as defined above) with arterial blood gas samples taken at rest and every 2 minutes during exercise via a small catheter in the radial artery. After a sufficient period of rest (6 h), they underwent a constant workload CPET for 12 minutes at 25% of their maximal previously determined work load. In the unloaded pedaling period, the subjects breathed ambient air. In the first 4 minutes (stage 1) of loaded pedaling they breathed ambient air, then 2% CO_2/21% O_2 balanced with N_2 during the next 4 minutes (stage 2), and then ambient air again for the last 4 minutes (stage 3). Whenever possible the constant workload CPET was repeated at least 1 hour later with 1% CO_2 at stage 2. During constant workload CPET

patients breathed through a T-shaped tube connected to 1-way inspiratory and expiratory valves. The former was connected to a large low pressure balloon filled with room air or the 1% or 2% CO_2 mixture, as required by the protocol. Arterial blood samples were collected at the end of each stage. In 7 patients randomly selected, the constant work test was repeated with the use of a 1% CO_2 mixture with the same temporal sequence. That night, all patients underwent an overnight respiratory monitoring study with measurement of nasobuccal air flow, chest and abdominal movement, oxygen saturation (SaO_2), and heart rate with the use of the Pamela Sleep Recorder (Medatecs, Brussels, Belgium).

Day 2

The next day, patients repeated the ramp CPET with arterial blood gas samples following the day 1 protocol 1 hour after the administration of 500 mg intravenous acetazolamide. In this protocol, the addition of inhaled CO_2 in the 2nd phase was not studied. Thereafter, treatment with 500 mg acetazolamide every 8 hours was started.

Day 3

On the 3rd day the patients again underwent the same testing as on day 2, but now after having received a total of 2 g acetazolamide (500 mg intravenously on day 1, followed by 3 500 mg oral doses every 8 hours). Then overnight respiratory event monitoring was again performed.

We analyzed the following ramp CPET parameters performed under the 3 different conditions (basal, and after ''acute'' and ''prolonged'' acetazolamide administration): VO_2 (mL/min), VO_2/kg (mL min^{-1} kg^{-1}), VCO_2 (mL/min), V_E (L/min), $PetCO_2$ (mm Hg), end-tidal O_2 ($PetO_2$; mm Hg), Vt (L), respiratory rate (RR; breaths/min), heart rate (HR; beats/min), O_2 pulse (VO_2/HR), work load achieved (W), and exercise tolerance (min). Peak exercise HR and gas exchange data were averaged over 30-second intervals. During exercise, we also recorded the kinetics of V_E/VCO_2 (ventilatory equivalents for CO_2) and the VO_2/work relationships. The PB duration was determined from the beginning of exercise (% of total exercise duration); number of cycles of PB during exercise, length of the first cycle of PB during exercise (s), V_E and Vt measurements at peak and nadir of PB cycles (mean of the first 3 cycles), and maximum value of Vt and V_E during exercise and at PB disappearance were also determined. Arterial blood gas analysis included measurement of pH, PO_2, PCO_2, HCO_3^-, and $SaO_{2\%}$.

During constant work rate CPET, we analyzed the following parameters at the end of the 4th, 8th, and 12th minutes: presence of PB during each exercise stage, peak and nadir values of V_E and Vt, mean values during CO_2 inhalation if PB disappeared, peak and nadir of the cycles if not, and the maximum values of Vt and V_E, along with arterial blood gas values.

To determine the disappearance of PB during both ramp and constant work rate exercise tests, we considered Vt as reference variable and defined PB cessation when the amplitude of V_E swings was $<10\%$. To do so, data were evaluated by visual inspection and graphically measured. An example is presented in Figure 4 (bottom).

We analyzed the sleep respiratory events, recorded both in the basal condition and after prolonged administration of acetazolamide with the use of the following criteria. Apnea was defined as cessation of air flow that lasted $\geq$10 seconds. Central apnea was identified by air flow cessation together with absence of thoraco-abdominal movements, whereas obstructive apnea was defined as air flow cessation in the presence of thoraco-abdominal movements. Hypopnea was defined as a $\geq$50% decrease in the sum of thoraco-abdominal movements lasting $\geq$10 seconds followed by a reduction of SaO_2 of $\geq$4%. The presence of PB during sleep was visually assessed.[7] Specifically, the presence of PB during sleep was visually assessed considering PB to be an oscillatory pattern in ventilation with a period of $\sim$60 s characterized by phases of hyperventilation and central apnea or hypopnea.[10] From these data we calculated the apnea/hypopnea index, apnea mean duration time, mean SaO_2 during sleep, mean nadir SaO_2 during sleep, and time with SaO_2 $<90\%$.

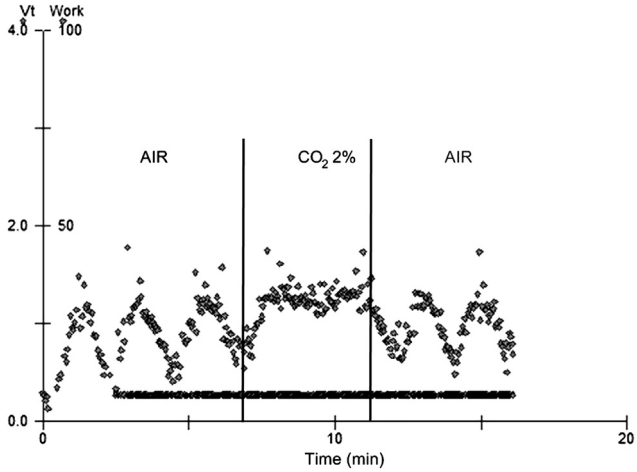

Fig. 2. Example of a constant workload test with disappearance of periodic breathing during 2% CO_2 inhalation. Vt, tidal volume.

Statistical Analysis

Data are presented as mean $\pm$ SD. Analysis of variance was used for repeated measurements. Data were reported in an Excel data file and analyzed with SPSS software (version 10.0; SPSS, Chicago, Illinois). Comparisons were made with the use of Student *t* paired test with Bonferroni corrections for initial and final values and for peak and nadir values, and a *P* value of $<.05$ was considered to be significant.

Results

The characteristics of the 20 study patients are summarized in Table 1. All were male with a mean age of 69 years with severe HF (mean LVEF 27%, peak VO_2 12.4 $\pm$ 4.7 mL kg^{-1} min^{-1}, VE/VCO_2 51.7 $\pm$ 7.3), and 35% had ischemic and 65% nonischemic etiologies. Typical for the therapy of this group, most were on beta-blockers, diuretics, and antiangiotensin therapies. Other medications used in $\leq$50% of the patients included digoxin, amiodarone, mineralocorticoid antagonists, and acetylsalicylic acid. Acetazolamide treatment did not influence diuresis, body weight, or serum electrolytes. Indeed, before acetazolamide and at day 3, diuresis, body weight, and serum Na^+, K^+, and Cl^- were, respectively, 1,915 $\pm$ 500 mL/24 h and 1,919 $\pm$ 933 mL/24 h, 75 $\pm$ 53 kg and 75 $\pm$ 53 kg, 140 $\pm$

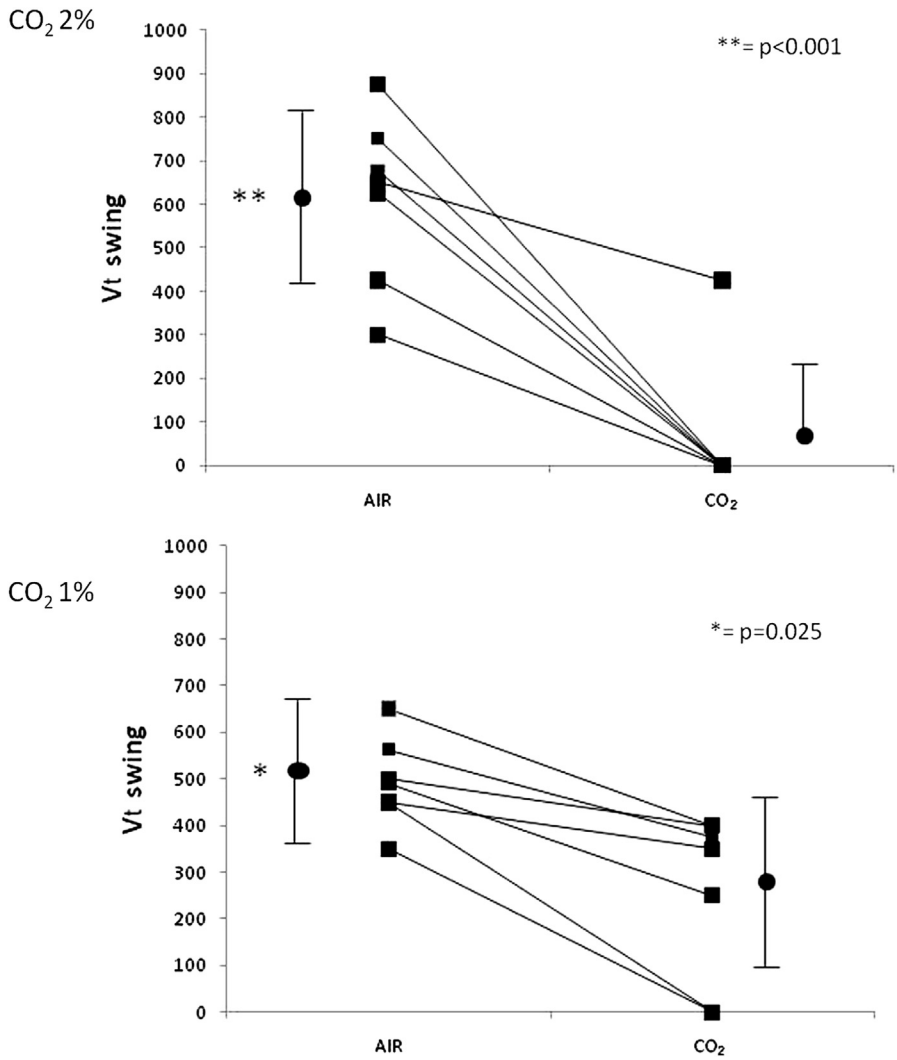

Fig. 3. Swing (difference between peak and nadir) of tidal volume (Vt) at constant-workload cardiopulmonary exercise test during air and 2% (top) and 1% (bottom) inhalation of CO_2 in the 7 patients who performed both tests.

0 meq/L and 139 ± 9 meq/L, 4.2 ± 2.5 meq/L and 4.0 ± 0.4 meq/L, and 104 ± 4 meq/L and 105 ± 5 meq/L.

Effects of CO_2 Inhalation on PB During Exercise

V_E (Table 2; Figs. 2 and 3). At rest, before constant work rate exercise (while sitting on the bike), and during ambient air breathing (stage 1), PB was evident in all of the patients. With 2% CO_2 inhalation (stage 2), PB disappeared in all but 1 case. In that patient, although PB was still detectable, the amplitude of Vt swing (difference between peak and nadir Vt) was markedly reduced (0.70 L during stage 1 and 0.35 L during stage 2). After resuming air inhalation in stage 3, PB recurred in all patients with the same pattern as before the CO_2 challenge. Peak and nadir values of Vt and V_E measured during air inhalation (stages 1 and 3), and mean values of Vt and V_E during 2% CO_2 inhalation (stage 2), when PB disappeared in the 20 patients who performed the constant rate test with 2% CO_2 inhalation, are presented in Table 2. An example of PB cessation with 2% CO_2 inhalation is shown in Figure 2. CO_2 inhalation was evaluated with 1% and 2% in 7 of the 20 subjects according to their willingness and personal availability at the end of a long working day. When compared with 2% CO_2, which suppressed PB in all but 1 subject, only 2 subjects breathing 1% CO_2 had disappearance of PB (Fig. 3). Although 1% CO_2 inhalation caused a reduction in the Vt variation, it was less than during 2% CO_2 inhalation (P = .010).

Gas Exchange (Table 3). Arterial blood gas values measured at the end of each exercise stage showed a statistically significant increase of PO_2 by 12 ± 2.6 mm Hg and of SaO_2 by 0.6 ± 6.6%, with a reduction of pH by −0.02 ± 2.02 (P = .001 for all), with 2% CO_2. With 1% CO_2 breathing (n = 7), we observed smaller similar directional changes in all values, but they did not reach statistical significance compared with the same patients breathing 2% CO_2.

Effects of Acetazolamide Administration

Data at Rest (Tables 4 and 5). No statistically significant differences were apparent in the cardiorespiratory parameters at rest (sitting on the bike) following the acute

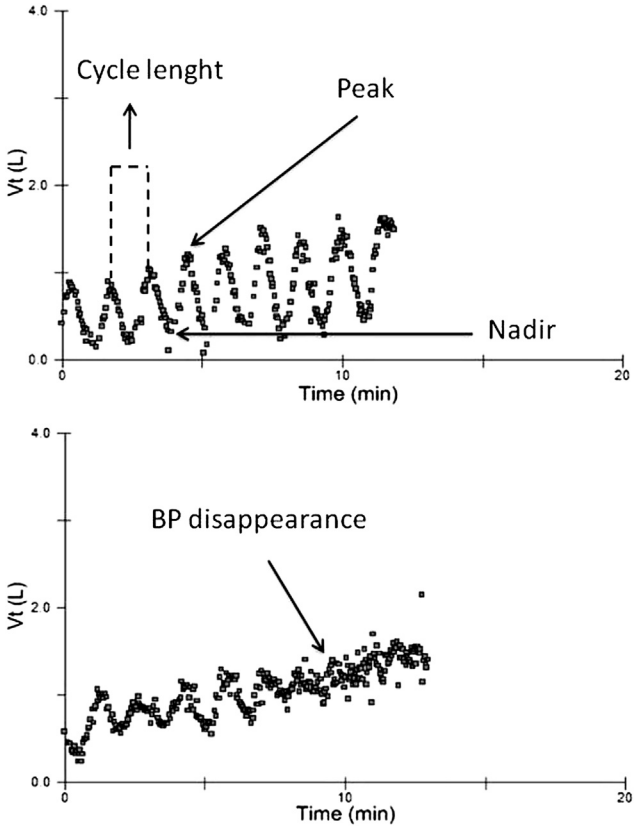

Fig. 4. Example of a ramp-workload cardiopulmonary exercise test in basal condition (top) and with earlier disappearance of periodic breathing after chronic administration of acetazolamide (bottom). Cycle length and tidal volume (Vt) peak and nadir during periodic breathing (BP) are indicated.

administration of acetazolamide, although V_E and Vt had suggestive upward trends. After prolonged administration (2 g over 24 h), V_E was increased significantly owing to an increase in Vt (+0.11 ± 1.13 L; $P = .003$), although the RR was not changed significantly. Consequently, $PetCO_2$ decreased (−2.59 ± 9.7 mm Hg; $P < .001$) and $PetO_2$ increased (+4.62 ± 2.43 mm Hg; $P = .001$). A slight, but significant, reduction in HR was also observed. No significant differences in resting VO_2 and VCO_2 were detected. Acute acetazolamide generated no statistically significant changes in any arterial blood gas parameter, most importantly no change in HCO_3^-, reflecting an insufficient time for the drug to have caused any quantitative renal bicarbonate loss. PCO_2 and PO_2 were slightly higher, suggestive of a higher V_E and a slight impairment of pulmonary CO_2 excretion from red cell and vascular endothelial cell CA inhibition,[12] but none of these changes reached statistical significance. In contrast, prolonged acetazolamide generated a statistically significant metabolic acidosis (lower pH and lower HCO_3^-) from renal CA inhibition resulting in a greater V_E and arterial PO_2. SaO_2 was not increased, reflecting a right shift in the hemoglobin dissociation curve arising from the Bohr Effect.

Table 1. Patient Characteristics

n	20
Sex (M/F)	20/0
Age (y)	69.1 ± 1.9
NYHA	2.9 ± 9.7
LVEF (%)	27.2 ± 7.9
LVDV (mL)	210.7 ± 64.4
LVDVI (mL/m^2)	112.6 ± 30.5
BMI (kg/cm^2)	24.5 ± 3.33
Therapy	
Beta-blockers	80%
ACE-I/ARB	80%
Diuretics	90%
Antialdosteronics	35%
Amiodarone	50%
ASA	40%
Digitalis	15%
Etiology	
Ischemic	35%
Nonischemic	65%

NYHA, New York Heart Association functional class; LVEF, left ventricular ejection fraction; LVDV, left ventricular diastolic volume; LVDVI, left ventricular diastolic volume index; BMI, body mass index; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ASA, acetylsalicylic acid.

Data at Peak Exercise (Tables 5 and 6). All subjects gave a full effort as indicated by achievement of a discernible ventilatory threshold (data not shown) and a fall in HCO_3^- of 3−4 mmol/L. Maximum HR was lower than age predicted owing to the high prevalence of beta-blocker use and possibly intrinsic chronotropic insufficiency typical in this patient group. No differences were observed among cardiorespiratory parameters at peak exercise after acute acetazolamide infusion compared with the control study. However, after prolonged administration of acetazolamide, maximum work load was significantly reduced by ∼10% ($P < .02$). We also observed a significant decrease in peak VO_2 and peak VCO_2. Total V_E at peak exercise did not change significantly, but V_E at any given work load was higher, as reflected in the lower $PetCO_2$ and higher V_E/VCO_2 values (data not shown). After prolonged acetazolamide, the V_E/VCO_2 slope increased. The arterial blood gas values during all stages of exercise and up to peak exercise are presented in Table 5. With acute acetazolamide administration, $PaCO_2$ was slightly higher and pH slightly lower compared with no treatment. With prolonged acetazolamide pH and HCO_3^- were statistically significantly lower and PaO_2 higher than with no treatment as well as different from acute acetazolamide treatment, reflecting the stronger ventilatory stimulus of the metabolic acidosis of prolonged administration.

PB During Exercise (Table 7). In the resting conditions, PB was present throughout the entire exercise in 6 patients, whereas it disappeared before the end of exercise in the remaining 14 patients. After acute administration of acetazolamide, PB disappeared altogether in 1 patient, and after prolonged administration PB disappeared in 7 patients. In the patients in whom PB was still detectable, its duration was significantly reduced after both acute and prolonged administration. As a percentage of exercise duration, PB was present 80 ± 26%, 65 ± 28%, and 43 ± 39% of the time before and after acute and prolonged acetazolamide administration, respectively ($P = .121$ basal vs

Table 2. Constant-Workload Exercise Test During Room Air and 2% CO_2 Breathing (n = 20)

	Stage 1 (Air) (n = 20)		Stage 2 (CO_2), No PB (n = 19)	Stage 3 (Air) (n = 20)	
	Peak	Nadir	Mean	Peak	Nadir
Vt (L)	1.18 ± 0.23	0.56 ± 0.16	1.29 ± 0.22	1.23 ± 0.21	0.71 ± 0.19
V_E (L/min)	27.9 ± 6.3	14.6 ± 4.0	33.3 ± 6.4	29.5 ± 6.4	18.9 ± 4.6

VE, ventilation; Vt, tidal volume; PB, periodic breathing. Data reported are those recorded at minutes 4 (stage 1), 8 (stage 2), and 12 (stage 3) of the constant-workload exercise.

acute; $P = .001$ basal vs prolonged; $P = .060$ acute vs prolonged). Vt and V_E values measured at the beginning of loaded pedaling (peak and nadir), at PB disappearance and as a maximum value observed throughout exercise, in basal condition and after acute and prolonged acetazolamide administration, are reported in Table 7. A significant reduction in number of PB cycles from the beginning of exercise and a significant increase in the PB cycle length (amplitude) were detected after acute and prolonged acetazolamide among patients in which PB was still present. An example of PB reduction after prolonged acetazolamide is shown in Figure 4.

Sleep Apnea (Table 8). Polysomnographic recordings of respiratory events during sleep were evaluatable both in the untreated condition and after prolonged administration of acetazolamide in 18/20 patients (in 1 patient the quality of recording after acetazolamide was not sufficient for evaluation, and 1 patient was intolerant of the monitoring equipment). In all recorded patients, significant sleep apnea was detectable in the untreated condition; however, in 2 patients the apnea/hypopnea index was below the cutoff of 10. The apnea/hypopnea index significantly decreased after prolonged administration of acetazolamide, whereas the average duration of events did not change significantly. We also observed a significant increase of nocturnal mean SaO_2 and of the time with SaO_2 <90%, whereas no difference was observed in mean nadir SaO_2.

Discussion

The important findings in this study are the following: 1) Inhalation of 2% CO_2 during submaximal exercise completely abolished PB during exercise in 95% of subjects with HF, but 1% CO_2 inhalation was effective in suppressing PB in only one-third; 2) with 2% CO_2 the subjects reached a higher mean V_E and Vt than the peak V_E and Vt of the PB cycles; 3) acetazolamide given acutely (intravenously) was relatively ineffective in suppressing PB during exercise, but when given over 24 hours, long enough to generate a metabolic acidosis, PB was suppressed in 7 patients; 4) in those patients on prolonged acetazolamide but without PB suppression, the number of PB cycles was reduced and the length of each cycle was increased; and 5) prolonged acetazolamide reduced exercise capacity by ~10% but improved sleep-disordered breathing with a reduction in the apnea-hypopnea index by 28%, leading to an overall higher mean arterial oxygenation and less time spent below an SaO_2 of 90%. These data confirm and extend the work of others showing that changes in

Table 3. Arterial Blood Gas Analysis During CO_2 Inhalation

					Bonferroni		
	Stage 1 (Air)	Stage 2 (CO_2)	Stage 3 (Air)	ANOVA	Stage 1 vs 2	Stage 2 vs 3	Stage 1 vs 3
2% CO_2 (n = 20)							
pH	7.46 ± 6.05	7.44 ± 4.03	7.45 ± 5.03	<.001	.001	.208	.307
PO_2 (mm Hg)	94.5 ± 50.5	107.4 ± 40.3	96.3 ± 31.5	<.001	<.001	<.001	.413
PCO_2 (mm Hg)	36.1 ± 1.9	37.2 ± 2.5	36.4 ± 4.6	.376			
HCO_3^- (mmol/L)	26.3 ± 3.1	25.8 ± 8.0	26.0 ± 0.2	.437			
SaO_2 (%)	97.7 ± 7.8	98.3 ± 3.5	97.7 ± 7.9	.001	.001	.001	1.000
2% CO_2 (n = 7 [patients who also underwent 1% CO_2])							
pH	7.47 ± 7.07	7.45 ± 5.05	7.46 ± 6.03	.267			
PO_2 (mm Hg)	92.9 ± 93.2	106.7 ± 7.0	95.4 ± 44.0	.020	.009	.054	.524
PCO_2 (mm Hg)	35.4 ± 4.5	35.9 ± 9.5	36.1 ± 1.5	.804			
HCO_3^- (mmol/L)	26.3 ± 3.6	25.4 ± 4.3	26.2 ± 2.1	.703			
SaO_2 (%)	97.7 ± 7.9	98.4 ± 4.2	97.7 ± 7.1	.183			
1% CO_2 (n = 7)							
pH	7.47 ± 7.05	7.45 ± 5.04	7.46 ± 6.04	.373			
pO_2 (mm Hg)	96.6 ± 60.8	100.6 ± 62.1	98.9 ± 90.6	.401			
pCO_2 (mm Hg)	32.8 ± 8.0	34.5 ± 55.0	35.4 ± 4.6	.150			
HCO_3^- (mmol/L)	24.8 ± 8.5	25.0 ± 0.1	25.8 ± 8.9	.505			
SaO_2 (%)	98.0 ± 0.7	98.1 ± 1.7	98.0 ± 0.7	.444			

ANOVA, analysis of variance; PO_2, oxygen partial pressure; PCO_2, carbon dioxide partial pressure; HCO_3^-, bicarbonate; SaO_2, oxygen saturation.

Table 4. Ramp-Protocol CPET: Data at Rest

					Bonferroni		
	No therapy	Acute	Chronic	ANOVA	No Therapy vs Acute	No Therapy vs Chronic	Acute vs Chronic
VO_2 (mL/min)	260 ± 55	251 ± 82	258 ± 62	.87			
VO_2/kg (mL kg^{-1} min^{-1}	4.2 ± 2.3	3.5 ± 5.6	3.8 ± 8.6	.629			
VCO_2 (mL/min)	203 ± 36	228 ± 88	225 ± 54	.068			
V_E (L/min)	11.7 ± 7.0	13.0 ± 0.0	13.8 ± 8.8	.001	.13	.001	.593
Vt (L)	0.56 ± 6.10	0.60 ± 0.09	0.67 ± 7.14	.003	.075	.002	.062
$PetCO_2$ (mm Hg)	29.4 ± 4.3	28.9 ± 9.4	26.8 ± 8.9	<.001	1	<.001	.002
$PetO_2$ (mm Hg)	112.9 ± 9.2	114.2 ± 2.5	117.5 ± 5.7	.001	.673	.001	.019
RR	21.0 ± 0.7	21.8 ± 8.6	22.3 ± 3.7	.271			
HR	73 ± 35	71 ± 12	69 ± 93	.016	.741	.019	.106
O_2 pulse (mL/beat)	3.6 ± 6.7	3.8 ± 8.0	4.0 ± 0.1	.082			

ANOVA, analysis of variance; VO_2, oxygen consumption; VCO_2, CO_2 production; V_E, ventilation; Vt, tidal volume; $PetCO_2$, end-tidal pressure of CO_2; $PetO_2$, end-tidal pressure of O_2; RR, respiratory rate (breaths/min); HR, heart rate (beats/min).

prevailing PCO_2, acid-base balance, and CO_2 reaction kinetics act to reduce PB in HF.

The regulation of breathing by the CNS is a complex process and arises from the medullary respiratory center, the output of which is influenced by a variety of factors, including cortical stimulation during the awake state, afferent signaling from the peripheral and central chemoreceptors, arterial baroreceptors, lung stretch receptors, musculoskeletal metaboreceptors, and numerous circulating vasoactive mediators that are altered in HF.[3] In addition to these tonic influences, time-dependent differences in arrival of these signals at the peripheral and central chemoreceptors and thence to the medullary respiratory controller also may be involved in stability or instability in breathing.[17] Of the several mechanisms postulated to cause PB in HF, whether in sleep, wakefulness, or exercise, alterations involving changes in CO_2 have received considerable attention. Experimental manipulations of CO_2 and acid-base status by CO_2 inhalation (as in the present study) and dead-space addition[7] during exercise that reduce or

Table 5. Effect of Acetazolamide on Arterial Blood Gas Values

						Bonferroni		
	Minute	Basal	Acute	Chronic	ANOVA	No Therapy vs Acute	no Therapy vs Chronic	Acute vs Chronic
pH	0	7.47 ± 7.05	7.45 ± 5.04	7.42 ± 2.05	<.001	.58	<.001	.00
	2	7.47 ± 7.04	7.45 ± 5.04	7.42 ± 2.04	<.001	.04	<.001	.00
	4	7.46 ± 6.04	7.45 ± 5.04	7.42 ± 2.04	<.001	.25	<.001	<.001
	6	7.46 ± 6.04	7.45 ± 5.03	7.41 ± 1.04	<.001	.77	<.001	<.001
	8*	7.47 ± 7.04	7.45 ± 5.03	7.42 ± 2.04	.004	.37	.003	.01
	Peak	7.47 ± 7.04	7.46 ± 6.03	7.40 ± 0.04	<.001	1.00	<.001	<.001
PO_2 (mm Hg)	0	92.8 ± 81.6	95.00 ± 03.4	101.2 ± 20.5	<.001	.89	<.001	.02
	2	93.6 ± 65.3	92.37 ± 72.8	98.6 ± 11.4	.008	1.00	.012	.02
	4	91.5 ± 53.3	93.47 ± 75.2	101.4 ± 41.6	.001	1.00	.001	.00
	6	95.5 ± 54.6	95.79 ± 94.8	102.5 ± 53.8	<.001	1.00	<.001	<.001
	8*	101.2 ± 24.2	102.53 ± 36.2	104.3 ± 4.6	.001	1.00	.117	.00
	Peak	102.9 ± 98.3	104.57 ± 77.4	107.0 ± 04.6	.015	1.00	.068	.01
PCO_2 (mm Hg)	0	36.7 ± 7.8	37.44 ± 4.2	35.4 ± 4.6	.09			
	2	35.9 ± 9.3	37.76 ± 6.9	35.3 ± 3.1	.041	.193	1.000	.038
	4	36.0 ± 0.9	37.09 ± 9.7	35.5 ± 3.2	.118			
	6	35.5 ± 5.1	36.82 ± 2.5	35.7 ± 7.4	.29			
	8*	33.0 ± 0.6	35.75 ± 5.2	34.3 ± 3.1	.022	.063	.881	.020
	Peak	32.6 ± 6.9	32.96 ± 6.6	34.3 ± 3.0	.584			
HCO_3^- (mmol/L)	0	26.8 ± 8.2	26.68 ± 8.1	23.3 ± 2.3	<.001	1.00	<.001	<.001
	2	26.6 ± 6.4	26.52 ± 2.1	23.2 ± 2.1	<.001	1.00	<.001	<.001
	4	26.3 ± 3.9	26.18 ± 8.0	23.4 ± 2.0	<.001	1.00	<.001	<.001
	6	26.0 ± 2.6	26.06 ± 6.5	23.2 ± 2.1	<.001	1.00	<.001	<.001
	8*	24.6 ± 6.6	25.65 ± 5.3	22.7 ± 7.1	<.001	.68	<.001	<.001
	Peak	23.6 ± 6.5	24.19 ± 9.9	21.7 ± 7.1	<.001	1.00	.004	<.001
SaO_2 (%)	0	97.5 ± 5.1	97.5 ± 5.0	97.92 ± 2.7	.127			
	2	97.3 ± 3.7	97.3 ± 3.0	97.69 ± 9.9	.109			
	4	97.3 ± 3.4	97.2 ± 2.7	97.88 ± 8.8	.075			
	6	97.5 ± 5.2	97.6 ± 6.0	97.82 ± 2.9	.067			
	8*	97.9 ± 9.0	98.0 ± 0.9	97.98 ± 8.9	.221			
	Peak	97.7 ± 7.4	98.0 ± 0.2	98.00 ± 0.1	.111			

Abbreviations as in Table 3.
*n = 14.

Table 6. Ramp-Protocol CPET: Peak Exercise Data

					Bonferroni		
	No Therapy	Acute	Chronic	ANOVA	No Therapy vs Acute	No Therapy vs Chronic	Acute vs Chronic
Work load (W)	61.3 ± 32.1	58.9 ± 92.0	55.9 ± 90.9	.021	.311	.019	.051
Exercise tolerance (min)	9.6 ± 6.6	9.2 ± 2.7	8.8 ± 8.8	.086			
VO_2 (mL/min)	920 ± 019	862 ± 232	849 ± 908	.045	.121	.036	1
VO_2/kg (mL kg^{-1} min^{-1})	12.4 ± 4.7	11.5 ± 5.6	11.5 ± 5.0	.043	.065	.054	1
VO_2 % of predicted value	46 ± 61	44 ± 42	43 ± 31	.039	.11	.032	1
VCO_2 (mL/min)	945 ± 541	874 ± 473	836 ± 622	.02	.151	.014	.627
VE (L/min)	47.4 ± 4.6	43.2 ± 21.4	45.7 ± 7.6	.077			
Vt (L)	1.33 ± 3.25	1.27 ± 7.25	1.39 ± 9.25	.031	.516	.341	.023
$PetCO_2$ (mm Hg)	27.6 ± 6.9	26.6 ± 6.7	24.3 ± 3.0	<.001	.06	<.001	.001
$PetO_2$ (mm Hg)	120.4 ± 4.4	120.4 ± 4.6	122.3 ± 3.2	.121			
RR	33.1 ± 1.3	32.7 ± 7.1	31.3 ± 3.1	.08			
HR	105 ± 51	103 ± 31	98 ± 80	.028	1	.02	.158
O_2 pulse (mL/beat)	9.4 ± 4.9	8.4 ± 4.2	8.8 ± 8.1	.034	.477	.069	.069
VE/VCO_2 at peak	51.7 ± 9.3	51.0 ± 9.1	56.5 ± 11.8	.022	1	.026	.072
Slope							
VE/VCO_2	39.0 ± 0.7	39.7 ± 7.1	43.5 ± 5.2	.022	1	.015	.12
VO_2/work (mL min^{-1} W^{-1})	8.9 ± 9.7	9.3 ± 3.7	8.9 ± 9.7	.334			

Abbreviations as in Tables 3 and 4.

abolish PB appear to be explained well by an increase in the eupneic PCO_2 to apneic PCO_2 threshold. Both maneuvers, by raising eupneic PCO_2, increase this difference and prevent or minimize the potential that any period of increased V_E, by whatever stimulus, will drive arterial PCO_2 below the apneic threshold. A fall below this threshold initiates a cessation of breathing that is ultimately ended when the combined strong stimuli of a falling arterial PO_2 and rising arterial PCO_2 evoke a brisk hyperventilatory response that then drives the PCO_2 down again below the apneic threshold to set up a vicious cycle of PB.

Effects of Inhaled CO_2 on PB and Gas Exchange

Our finding that CO_2 inhalation during exercise abolishes PB in a dose-dependent manner is fully consistent with the paradigm that an elevation of eupneic PCO_2 without a change in the apneic PCO_2 threshold will act to stabilize breathing against a strong background of ventilatory stimulation such as exists in HF. This has already been demonstrated in these patients during sleep,[8–10] and we show for the first time the same efficacy in exercise. We also found that arterial PO_2 was significantly higher with inhaled CO_2, likely a result of both an increase in V_E and a reduction in ventilation-perfusion mismatching.[18] The tendency to PB may arise from an augmentation in the summed chemoreceptor inputs to respiratory drive, which are O_2 (peripheral) and CO_2 (peripheral and central) dependent. Although the slight rise in PCO_2 would be stimulating to ventilatory drive, the concurrent rise in PO_2 of 13 mm Hg (with 2% CO_2) or 4 mm Hg (with 1% CO_2) may exert a counterinhibitory effect via withdrawal of peripheral

Table 7. Effect of Acetazolamide on Periodic Breathing Cycle

					Bonferroni		
	Basal	Acute	Chronic	ANOVA	No Therapy vs Acute	No Therapy vs Chronic	Acute vs Chronic
V_E (L/min)							
Peak (*)	22.6 ± 6.9 (n = 20)	22.0 ± 0.3 (n = 19)	20.8 ± 8.3 (n = 13)	.443			
Nadir (*)	8.0 ± 0.6 (n = 20)	9.6 ± 6.9 (n = 19)	8.5 ± 5.7 (n = 13)	.014	.012	.157	.604
Disappearance	32.8 ± 80.2 (n = 14)	28.7 ± 7.4 (n = 17)	32.2 ± 20.7 (n = 13)	.687			
Maximum	48.4 ± 40.9 (n = 20)	43.9 ± 91.2 (n = 19)	45.4 ± 42.9 (n = 13)	.248			
Vt (L)							
Peak (*)	1.0 ± 0.2 (n = 20)	0.9 ± 9.3 (n = 19)	0.9 ± 9.2 (n = 13)	.509			
Nadir (*)	0.3 ± 3.1 (n = 20)	0.4 ± 4.1 (n = 19)	0.4 ± 4.1 (n = 13)	.021	.133	.014	.169
Disappearance	1.3 ± 3.2 (n = 14)	1.1 ± 1.3 (n = 17)	1.1 ± 1.3 (n = 13)	.427			
Maximum	1.5 ± 5.2 (n = 20)	1.4 ± 4.2 (n = 19)	1.5 ± 5.3 (n = 13)	.348			
No. of cycles	5.0 ± 0.9 (n = 20)	3.6 ± 6.9 (n = 19)	2.9 ± 9.9 (n = 13)	.002	0.157	.001	.18
Length of 1st cycle of exer. (s)	83.1 ± 16 (n = 20)	88.9 ± 99.9 (n = 19)	101.9 ± 99.6 (n = 13)	.003	1	.002	.042

Abbreviations as in Table 4.
*Peak and nadir were calculated as mean value of the first 2 cycles from the beginning of exercise.

Table 8. Effect of Acetazolamide on Sleep Apnea

	Basal	Chronic Therapy	*P* Value
Apnea/hypopnea Index (events/h)	30.8 ± 13.8	21.1 ± 16.9	.003
Mean apnea duration (s)	26.9 ± 6.1	28.4 ± 7.0	.431
Mean SaO_2 (%)	93.2 ± 2.3	94.1 ± 2.2	.005
Minimal SaO_2 (%) (nadir)	86.6 ± 2.5	86.1 ± 4.6	.677
Time at SaO_2 <90% (min)	65.6 ± 86.1	37.1 ± 54.8	.035
% of time at SaO_2 <90%	12.76 ± 15.5	9.6 ± 15.5	.031

SaO_2, oxygen saturation.

chemoreceptor afferent signaling. Although O_2-sensitive carotid body output is not generally thought to be important when PaO_2 is >70 mm Hg, owing to the very hyperbolic nature of the hypoxic ventilatory response, some peripheral chemoreceptor activity is still present at normal physiologic PaO_2 (and more so in HF patients) and can be suppressed with further elevation of PaO_2 beyond 100 mm Hg.[19]

Effects of Acetazolamide on Gas Exchange, Exercise Performance, PB, and Sleep

We found that when acetazolamide is given acutely and patients are studied before the development of any appreciable metabolic acidosis (Table 5) there is, compared with the basal test, a statistically nonsignificant increase in resting V_E (Table 4) associated with an increase in PaO_2 as well as $PaCO_2$. These changes reflect the mild hyperventilatory stimulus of slight CO_2 retention arising from partial red cell CA inhibition and complete vascular endothelial cell CA inhibition[12,20] that occur with the transient high free drug levels reached with intravenous administration. The same pattern of gas exchange and increased V_E relative to CO_2 production (V_E/VCO_2) at rest is evident during exercise. Acute acetazolamide caused a slight reduction in peak VO_2 and work load similar to that seen in healthy subjects,[21] reflecting a possible limiting effect on exercise of a slightly higher ventilatory demand and a greater degree of CO_2 retention and acidosis at the muscle (cardiac and skeletal) level that is not accurately reflected by arterial blood gas values.[22]

The trends noted above with acute acetazolamide on gas exchange and exercise performance were greater and reached statistical significance with the continued oral administration of the drug over the subsequent 24 hours. The patients had the expected fall in bicarbonate and lower arterial pH from renal loss of bicarbonate.[12] In this situation of lower free drug levels with oral administration and a metabolic acidosis, V_E was higher at rest and at all levels of exercise. As a result, arterial PCO_2 was decreased and PaO_2 was much higher. The lack of arterial PCO_2 elevation compared with that observed with acute intravenous administration is consistent with less red cell CA inhibition and thus less impairment of pulmonary CO_2 excretion.[22] Despite better gas exchange, peak exercise was reduced, again likely owing to the acidosis and greater ventilatory demand causing a greater proportion of the cardiac output necessary to serve the respiratory muscles and diverting blood flow from the exercising locomotor muscles,[23] as is observed in healthy humans given acetazolamide orally over 24 hours.[24]

Acetazolamide acutely and after 24 hours of administration was effective in suppressing PB during exercise, but not as potently as 2% inhaled CO_2. We chose to study 1% and 2% inhaled CO_2 to recreate the slight degree of CO_2 retention expected with acetazolamide, particularly with the acute intravenous dosing. In this respect we were successful, because the elevations in $PaCO_2$ with 2% inhaled CO_2 of 1.11 mm Hg (Table 3) and with acute acetazolamide of 1.05 mm Hg (Table 5) at roughly equivalent exercise levels were similar. However, this was not the case with prolonged acetazolamide, in which the $PaCO_2$ was, in fact, lower and yet PB suppression was even greater with chronic acetazolamide than with acute acetazolamide. Although the slightly higher $PaCO_2$ with acute dosing of acetazolamide and partial suppression of PB fits with a drug-induced widening of the eupneic-apneic PCO_2 difference, the paradox of even greater PB suppression associated with lower $PaCO_2$ with chronic acetazolamide requires explanation. The paradox was resolved by Nayakama et al,[25] who showed that in sleeping dogs given acetazolamide and studied after a metabolic acidosis was established did widen the eupneic-apneic PCO_2 difference. This was brought about by the increased tonic hyperventilation driving down the apneic PCO_2 to a greater extent than eupneic PCO_2 was lowered. This was also shown for almitrine, a nonhypoxic peripheral chemoreceptor stimulant, but not for hypoxia itself.

CA is present in many tissues, including the brain and chemoreceptors,[12] and we must consider other actions by which acetazolamide might be effective in PB suppression both in exercise and during sleep. As mentioned above, PB may have as one of its contributors a mismatch or temporal dyssynchrony of inputs from the peripheral chemoreceptors (largely O_2 sensing, but also CO_2/pH sensing) and the central chemoreceptors (only CO_2/pH sensing). One source of this mismatch (a delay in the time of transit of blood from the lungs to the chemoreceptors) could be differences in cardiac output with acetazolamide, but studies in animals and healthy humans show no reduction of cardiac output at any exercise level.[26,27] The other manner in which the rate of afferent signaling might be altered relates to the effects of CA inhibition in the chemoreceptors themselves. CA inhibitors slow the rate at which the peripheral chemoreceptors respond to a change in pO_2 and reduce the magnitude of the final response[20,28] as well as the rate of response to changes in CO_2.[28] In similar fashion, the rate of response to CO_2 in the central chemoreceptors also is slowed by acetazolamide.[29] Slowing of these responses may be sufficient enough that in the event of a random increase or decrease in V_E causing a change in $PaCO_2$ and PaO_2, the tendency of the respiratory controller to overreact and then underreact in response will be dampened or abolished, such as is the case in high-altitude PB.[30,31]

Our results showing PB suppression in exercise with acetazolamide differ somewhat from those of Fontana et al,[14] who failed to find any effect, despite showing, as we did, reduction in PB and central apneas during sleep in these patients (see also Javaheri[13]) and reduction in maximal exercise capacity. They used a lower dose of prolonged acetazolamide (250 mg every 12 hours for 4 days) in contrast to our higher dosing of 500 mg every 8 hours over 24 hours. As a result, free drug levels and degree of tissue CA inhibition were considerably higher in our patients.[15] Although no arterial blood gas measurements were taken by Fontana et al,[14] we do not think the magnitude of metabolic acidosis was any different, because full renal CA inhibition is reached at very low doses (1−2 mg/kg) owing to drug concentration in the urine by renal tubular secretion.[12] Instead, the difference in exercise PB responses must be dependent on greater and more critical inhibition of CA in the chemoreceptors and brain and thus require higher doses than the lower doses of acetazolamide that are effective in suppression of sleep breathing irregularities.

The heart contains several isoforms of CA at very low concentrations,[32,33] but their roles remain uncertain given that even under the maximal demands of heavy exercise, there is no reduction of cardiac output[26] or evidence of reduced myocardial contractility.[34] Furthermore, with more than 5 decades of use in several chronic conditions, such as glaucoma, there have been no reports of adverse direct cardiac effects. In fact, more recent work suggests that acetazolamide may prevent and reverse cardiomyocyte hypertrophy[33,35] by causing a very slight intracellular acidosis[36] that opposes the intracellular alkalizing hypertrophic stimulus initiated by alpha-adrenergic activation.[33] This reassuring safety record would support a trial of acetazolamide in HF patients with PB and central sleep apnea. The benefits, particularly during sleep, of many hours of regular breathing might reduce neurosympathetic activation and perhaps alter the course of myocardial hypertrophic remodeling and the even more relevant risk of sudden cardiac death.[37]

A few study limitations should be acknowledged. First, we strongly encouraged patients to perform a maximal effort; however, the test was self-ended by the patients when they felt that they had reached their maximal possible performance. In HF patients studied with CPET, peak exercise respiratory ratio (VCO_2/VO_2) >1.1 is used as an index of maximal or near-maximal exercise performance. However, with PB, the respiratory ratio is cyclic with a wide variation, so that its value at peak exercise as an index of maximal metabolic effort has no meaning. Therefore, we can only rely on the patient's cooperation. Second, we studied the effects of acetazolamide for 2 days. The safety and the effects on respiratory parameters of acetazolamide with more chronic administration in chronic HF patients remain unknown. Our observation should not be used to suggest chronic treatment with acetazolamide in HF patients with exercise PB until a proper clinical trial is conducted. Third, we studied severe HF patients only in a stable clinical condition. The effects of acetazolamide administration in patients with an unstable clinical state or with relevant clinical comorbidities, such as lung disease or renal failure, is also unknown.

In conclusion, we have shown for the first time that both inhaled CO_2 and acetazolamide favorably alter PB during exercise in HF patients, and we add further to the evidence of a benefit of acetazolamide during sleep. The mechanism of action of both inhaled CO_2 and acetazolamide to reduce PB involves increasing the eupneic-apneic PCO_2 difference so that any spontaneous variability of V_E does not so easily drive arterial PCO_2 below the apneic threshold. Furthermore, acetazolamide may also act to stabilize breathing by slowing the response dynamics of chemoreceptor signaling to the respiratory control center and so reduce the tendency of overresponse to small fluctuations in arterial PCO_2 and PO_2. Our findings and those of others suggest that whether breathing is stabilized or destabilized in HF patients is a complicated scenario dependent on the causes of background heightened ventilatory drive, the prevailing arterial and tissue partial PCO_2 and PO_2, and the speed at which changes in these gas values are sensed at sites of chemoreception, signaled, and then processed at the respiratory control center.

Disclosures

None.

References

1. Corra U, Pistono M, Mezzani A, Braghiroli A, Giordano A, Lanfranchi P, et al. Sleep and exertional periodic breathing in chronic heart failure: prognostic importance and interdependence. Circulation 2006;113:44−50.
2. Sun XG, Hansen JE, Beshai JF, Wasserman K. Oscillatory breathing and exercise gas exchange abnormalities prognosticate early mortality and morbidity in heart failure. J Am Coll Cardiol 2010;55:1814−23.
3. Dhakal BP, Murphy RM, Lewis GD. Exercise oscillatory ventilation in heart failure. Trends Cardiovasc Med 2012;22:185−91.
4. Pinna GD, Maestri R, Mortara A, La Rovere MT, Fanfulla F, Sleight P. Periodic breathing in heart failure patients: testing the hypothesis of instability of the chemoreflex loop. J Appl Physiol (1985) 2000;89:2147−57.
5. Ben-Dov I, Sietsema KE, Casaburi R, Wasserman K. Evidence that circulatory oscillations accompany ventilatory oscillations during exercise in patients with heart failure. Am Rev Respir Dis 1992;145(4 Pt 1):776−81.
6. Cherniack NS, Longobardo GS. Cheyne-stokes breathing. An instability in physiologic control. N Engl J Med 1973;288:952−7.
7. Agostoni P, Apostolo A, Albert RK. Mechanisms of periodic breathing during exercise in patients with chronic heart failure. Chest 2008;133:197−203.
8. Steens RD, Millar TW, Su X, Biberdorf D, Buckle P, Ahmed M, Kryger MH. Effect of inhaled 3% CO_2 on Cheyne-Stokes respiration in congestive heart failure. Sleep 1994;17:61−8.
9. Lorenzi-Filho G, Rankin F, Bies I, Douglas Bradley T. Effects of inhaled carbon dioxide and oxygen on Cheyne-Stokes respiration in patients with heart failure. Am J Respir Crit Care Med 1999;159(5 Pt 1):1490−8.

10. Giannoni A, Baruah R, Willson K, Mebrate Y, Mayet J, Emdin M, et al. Real-time dynamic carbon dioxide administration: a novel treatment strategy for stabilization of periodic breathing with potential application to central sleep apnea. J Am Coll Cardiol 2010;56:1832−7.
11. Hackett PH, Roach RC, Harrison GL, Schoene RB, Mills WJ Jr. Respiratory stimulants and sleep periodic breathing at high altitude. Almitrine versus acetazolamide. Am Rev Respir Dis 1987;135:896−8.
12. Swenson ER. Carbonic anhydrase inhibitors and ventilation: A complex interplay of stimulation and suppression. Eur Respir J 1998;12:1242−7.
13. Javaheri S. Acetazolamide improves central sleep apnea in heart failure: a double-blind, prospective study. Am J Respir Crit Care Med 2006;173:234−7.
14. Fontana M, Emdin M, Giannoni A, Iudice G, Baruah R, Passino C. Effect of acetazolamide on chemosensitivity, cheyne-stokes respiration, and response to effort in patients with heart failure. Am J Cardiol 2011;107:1675−80.
15. Teppema LJ, Dahan A. Acetazolamide and breathing. Does a clinical dose alter peripheral and central CO_2 sensitivity? Am J Respir Crit Care Med 1999;160(5 Pt 1):1592−7.
16. Corra U, Giordano A, Bosimini E, Mezzani A, Piepoli M, Coats AJ, Giannuzzi P. Oscillatory ventilation during exercise in patients with chronic heart failure: clinical correlates and prognostic implications. Chest 2002;121:1572−80.
17. Tkacova R, Niroumand M, Lorenzi-Filho G, Bradley TD. Overnight shift from obstructive to central apneas in patients with heart failure: role of PCO_2 and circulatory delay. Circulation 2001;103:238−43.
18. Swenson ER, Robertson HT, Hlastala MP. Effects of inspired carbon dioxide on ventilation-perfusion matching in normoxia, hypoxia, and hyperoxia. Am J Respir Crit Care Med 1994;149:1563−9.
19. Schultz HD, Marcus NJ. Heart failure and carotid body chemoreception. Adv Exp Med Bio 2012:387−95.
20. Swenson ER, Hughes JM. Effects of acute and chronic acetazolamide on resting ventilation and ventilatory responses in men. J Appl Physiol 1993;74:230−7.
21. Kowalchuk JM, Heigenhauser GJ, Sutton JR, Jones NL. Effect of acetazolamide on gas exchange and acid-base control after maximal exercise. J Appl Physiol 1992;72:278−87.
22. Swenson ER, Maren TH. A quantitative analysis of CO_2 transport at rest and during maximal exercise. Respir Physiol 1978;35:129−59.
23. Harms CA, Wetter TJ, McClaran SR, Pegelow DF, Nickele GA, Nelson WB, et al. Effects of respiratory muscle work on cardiac output and its distribution during maximal exercise. J Appl Physiol 1998;85:609−18.
24. Schoene RB, Bates PW, Larson EB, Pierson DJ. Effect of acetazolamide on normoxic and hypoxic exercise in humans at sea level. J Appl Physiol 1983;55:1772−6.
25. Nakayama H, Smith CA, Rodman JR, Skatrud JB, Dempsey JA. Effect of ventilatory drive on carbon dioxide sensitivity below eupnea during sleep. Am J Respir Crit Care Med 2002;165:1251−60.
26. Jonk AM, van den Berg IP, Olfert IM, Wray DW, Arai T, Hopkins SR, Wagner PD. Effect of acetazolamide on pulmonary and muscle gas exchange during normoxic and hypoxic exercise. J Physiol 2007;579(Pt 3):909−21.
27. Vengust M, Staempfli H, Swenson ER, et al. Acetazolamide attenuates transvascular fluid flux in equine lungs during intense exercise. J Physiol 2013;591(Pt 18):4499−513.
28. Iturriaga R, Mokashi A, Lahiri S. Dynamics of carotid body responses in vitro in the presence of CO_2-HCO_3^-: role of carbonic anhydrase. J Appl Physiol 1993;75:1587−94.
29. Coates EL, Li AH, Nattie EE. Acetazolamide on the ventral medulla of the cat increases phrenic output and delays the ventilatory response to CO_2. J Physiol 1991;441:433−51.
30. Berssenbrugge A, Dempsey J, Iber C, Skatrud J, Wilson P. Mechanisms of hypoxia-induced periodic breathing during sleep in humans. J Physiol 1983;343:507−24.
31. Swenson ER, Teppema LJ. Prevention of acute mountain sickness by acetazolamide: as yet an unfinished story. J Appl Physiol 2007;102:1305−7.
32. Swenson ER. Carbonic anhydrase and the heart. Cardiologia 1997;42:453−62.
33. Alvarez BV, Johnson DE, Sowah D, Soliman D, Light PE, Xia Y, et al. Carbonic anhydrase inhibition prevents and reverts cardiomyocyte hypertrophy. J Physiol 2007;579(Pt 1):127−45.
34. Geers C, Gros G. Contractile function of papillary muscles with carbonic anhydrase inhibitors. Life Sci 1995;57:591−7.
35. Brown BF, Quon A, Dyck JR, Casey JR. Carbonic anhydrase II promotes cardiomyocyte hypertrophy. Can J Physiol Pharmacol 2012;90:1599−610.
36. Vaughan-Jones RD, Spitzer KW, Swietach P. Intracellular ph regulation in heart. J Mol Cell Cardiol 2009;46:318−31.
37. Guazzi M, Raimondo R, Vicenzi M, Arena R, Proserpio C, Sarzi Braga S, Pedretti R. Exercise oscillatory ventilation may predict sudden cardiac death in heart failure patients. J Am Coll Cardiol 2007;50:299−308.