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.

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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

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($PetCO_2$) 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.

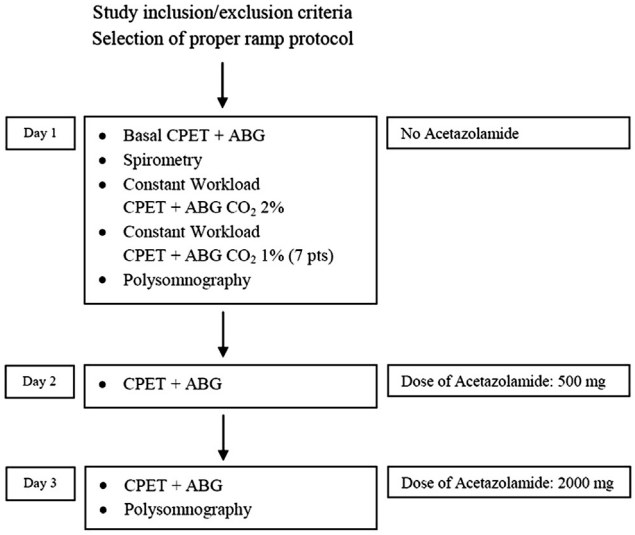

Fig. 1. Flow-chart of the tests performed. CPET, cardiopulmonary exercise test; ABG, arterial blood gas test.

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