ORIGINAL ARTICLE

Effects of device-guided slow breathing training on exercise capacity, cardiac function, and respiratory patterns during sleep in male and female patients with chronic heart failure

Kalina Kawecka-Jaszcz[1], Grzegorz Bilo[2,3], Tomasz Drożdż[1], Dorota Dębicka-Dąbrowska[1], Grzegorz Kiełbasa[1], Gabriella Malfatto[2], Katarzyna Styczkiewicz[1], Carolina Lombardi[2], Agnieszka Bednarek[1], Sabrina Salerno[2], Danuta Czarnecka[1], Gianfranco Parati[2,3]

1   I Department of Cardiology, Interventional Electrocardiology and Hypertension, Jagiellonian University Medical College, Kraków, Poland
2   Department of Cardiovascular, Neural and Metabolic Sciences, S. Luca Hospital, IRCCS Istituto Auxologico Italiano, Milan, Italy
3   Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

KEY WORDS

chronic heart failure,
sleep apnea, slow
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ABSTRACT

INTRODUCTION   Slow breathing training (SBT) has been proposed as a new nonpharmacologic treatment in patients with chronic heart failure (CHF).

OBJECTIVES   The aim of this study was to assess the effects of SBT on exercise capacity, hemodynamic parameters, and sleep respiratory patterns in a relatively large sample of CHF patients.

PATIENTS AND METHODS   A crossover open study was conducted. Patients completed, in a random order, 10- to 12-week SBT, with 2 15-minute sessions of device-guided SBT each day, reaching 6 breaths/min, and a 10- to 12-week follow-up under standard care. Clinical data collection, polysomnography, echocardiography, 6-minute walk test (6MWT), and laboratory tests were performed.

RESULTS   A total of 96 patients (74 men, 22 women) in New York Heart Association classes I–III, with an average age of 65 years and an ejection fraction (EF) of 31%, completed the study. Home-based SBT was safe. After training, EF and 6MWT distance improved (EF: 31.3% $\pm 7.3\%$ vs 32.3% $\pm 7.7\%$; $P = 0.030$; 6MWT: 449.9 ± 122.7 m vs 468.3 ± 121.9 m; $P < 0.001$), and the apnea–hypopnea index decreased (5.6 [interquartile range (IQR), 2.1; 12.8] vs 5.4 [IQR, 2.0; 10.8]; $P = 0.043$).

CONCLUSIONS   SBT improved physical capacity and systolic heart function; it also diminished sleep disturbances. The results support the benefits of SBT as a novel component of cardiorespiratory rehabilitation programs in patients with CHF.

INTRODUCTION   Chronic heart failure (CHF) has become one of the most widespread diseases and a principal cause of morbidity and mortality, due to the high prevalence of its main causes in aging societies, namely, hypertension and coronary heart disease.[1,2] Despite unquestionable progress in pharmacologic and device-based treatment, the mortality of CHF patients has only slightly improved in recent years,[3,4] and frequent hospitalizations[4] and poor quality of life[5] of these patients remain major health care issues. Especially in this latter aspect, cardiac rehabilitation programs based on physical exercise might prove particularly beneficial. However, their use in clinical practice remains limited because of the time and resources needed to achieve a satisfactory outcome. New nonpharmacologic home-based treatment options may thus be of particular interest in this regard. Among these options, respiratory training aimed at slowing the breathing rate, was proposed some years ago. A device for slow breathing training (SBT) was developed (RESPeRATE) in order to facilitate the patient in the potentially difficult task of maintaining

FIGURE 1 Study design; group I, started with slow breathing training (SBT); group II, started with standard care
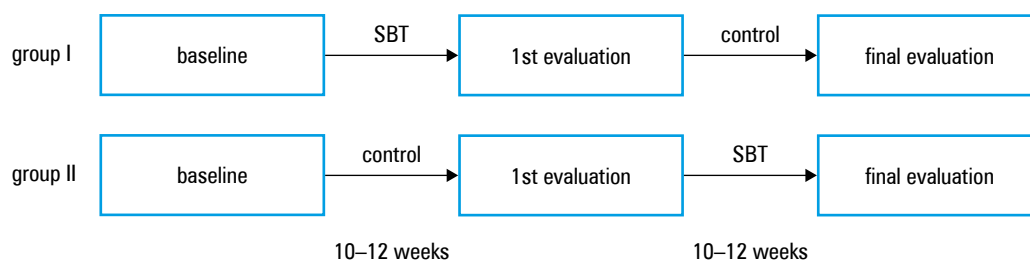
a constant number of breaths. This device guides the breathing exercise through visual and acoustic feedback, and its application has been recognized by the American Heart Association as a potentially useful nonpharmacologic approach for lowering blood pressure.[6]

The use of SBT has also been shown to be a feasible treatment option in the framework of the home-based rehabilitation of patients with CHF.[7] Our previously published data indicated that it is safe and does not significantly affect blood pressure values or the prevalence of orthostatic hypotension in these patients.[8] Moreover, preliminary data have demonstrated the usefulness of home-based rehabilitation in terms of improving both subjective (New York Heart Association [NYHA] class, breathlessness) and objective (exercise capacity, pulmonary function, and ventricular EF) parameters.[9-11] It was hypothesized that the favorable effects of SBT may be mediated by improved baroreflex sensitivity and respiratory mechanics.[9,10]

Respiratory abnormalities, from shallow breathing to Cheyne-Stokes periodicity, are very frequent in advanced CHF and their presence suggests a poor prognosis.[12] In particular, sleep-disordered breathing, mainly characterized by the presence of central apneas, is found in up to 76% of patients with systolic and diastolic heart failure[13] and, apparently, remains in a dose-dependent relationship with heart failure severity.[14] Intervention with positive airway pressure devices was shown to reduce the number of central apneas in CHF patients[15] and may improve some clinical parameters.[16] However, data from a recent trial suggest that adaptive servoventilation treatment is associated with higher mortality in CHF patients.[17]

Alternative therapeutic options to correct sleep-disordered breathing in CHF thus remain to be evaluated. In this context, no information is available on whether a training based on slow breathing during the day may improve abnormal patterns of respiration at night.

In summary, previous data indicate that SBT may be a simple and clinically useful adjunct to cardiac rehabilitation in CHF patients but stronger evidence is needed to support its clinical use. Therefore, we performed this study to assess the effects of SBT on clinical variables, including exercise capacity, hemodynamic parameters, and respiratory patterns during sleep in a relatively large sample of patients with CHF.

PATIENTS AND METHODS **Study design** The study, performed in 2 cardiology departments (Kraków, Poland and Milan, Italy), employed a crossover open trial design where patients, in a random order, underwent a 10- to 12-week SBT with the RESPeRATE device (InterCure Ltd., Lod, Israel) and a 10- to 12-week follow-up under standard care. Participants were identified by local investigators in the period between 2012 and 2015, and were consecutively assigned to intervention sequence starting with either SBT or standard care according to a previously prepared simple randomization list. In all patients, home sleep study, echocardiography, 6-minute walk test (6MWT), and laboratory tests were performed at baseline and after each study phase (FIGURE 1). Optimized pharmacologic treatment was maintained throughout the study. The study was performed in accordance with the 1975 Declaration of Helsinki for Human Research and approved by the Bioethical Committee of the participating institutions: Jagiellonian University Bioethical Committee and the Ethics Committee of Istituto Auxologico Italiano. Patients were included only if they gave their written informed consent. The study has been registered in the Polish National Science Centre (number 2011/03/B/NZ5/00 533).

Study population Adult patients with CHF fulfilling the following conditions were enrolled for this study: NYHA classes I–III; left ventricular EF (LVEF) lower than 40% in echocardiographic study; stable clinical conditions with no cardiovascular interventions over the previous 3 months; receiving stable pharmacologic treatment over the previous 4 weeks; sinus rhythm in 24-hour Holter monitoring; and ability to perform breathing exercises after supervised training. Patients after heart transplantation, patients who had received traditional cardiac rehabilitation within the previous 3 months, and patients presenting with serious chronic obstructive pulmonary disease, ventricular arrhythmias (tachycardia, fibrillation), or conduction abnormalities (second- and third-degree atrioventricular block) were excluded.

Slow breathing training (the RESPeRATE device) In the present study, patients were asked to undergo 2 separate 15-minute sessions of device-guided SBT with the RESPeRATE device throughout the 10- to 12-week period of SBT. The principles

of functioning of this device were described previously.[18] Briefly, after a "learning" phase of the patient's respiratory pattern, the device guides the patient's breathing by means of a musical pattern and gradually reduces breathing frequency to 6 breaths/min, while maintaining a desired inspiration/expiration time ratio.[8]

Echocardiography Echocardiography was performed using Vivid 7 Pro (General Electric, Fairfield, Connecticut, United States), with a 2.5-MHz probe by a single experienced operator who was blinded to the patients' allocation to experimental groups. One-dimensional, two-dimensional, pulse, and continuous Doppler, and pulsed-wave tissue Doppler imaging methods incorporating the measurement of individual phases of mitral annulus velocity were used. Each point of the protocol was recorded for at least 3 cardiac cycles during patients' steady breathing. The data were recorded, stored, and analyzed using the Echo-Pack system (General Electric). EF was calculated using the Simpson's formula. In the presence of tricuspid regurgitation, the tricuspid regurgitation pressure gradient and the value of right atrial pressure estimated on the basis of the width and the respiratory subsidence of the vena cava were used to assess the systolic pressure in the right ventricle. Right ventricular systolic pressure was calculated by adding the values of tricuspid regurgitation pressure gradient and right atrial pressure.[19]

Home sleep study Home sleep study was performed with Embletta Gold, an ambulatory overnight cardiorespiratory device (Embla, Broomfield, Colorado, United States), which recorded nasal/oral airflow (via a pressure cannula), chest and abdominal wall movements (via inductive belts), oxygen saturation (via a finger probe pulse-oximetry) and heart rate (via a CM5 device). A breathing event was defined as abnormal if: 1) a complete cessation of airflow lasting more than 10 seconds was present (apnea); or 2) a reduction in respiratory airflow greater than 50% and lasting more than 10 seconds and associated with a desaturation of 4% or higher (hypopnea) occurred. Obstructive apneas were defined by a reduction of respiratory airflow of over 50% for a minimum of 10 seconds, associated with paradoxical thoracic and abdominal motion and a desaturation of 4% or higher. Central apneas were defined by the absence/reduction of respiratory airflow for 10 seconds with an absence of thoracic and abdominal excursions and a desaturation of 4% or higher. The apnea–hypopnea index (AHI) was defined as the average number of apneas and hypopneas per hour of sleep. A sleep-related breathing disorder was diagnosed when the AHI was 5 or higher. Cheyne–Stokes respiration was characterized by the lack of air flow and respiratory effort followed by hyperventilation in a crescendo-decrescendo pattern.[20]

Six-minute walk test The 6MWT was performed in patients after a 10-minute resting period in a sitting position. Patients were asked to march at their own pace, on a flat and level surface in an empty corridor. They were informed about the progress of the test on regular basis; at the end of the 6-minute period, the total distance walked was measured. At baseline and after the test, blood pressure and oxygen saturation were also measured.[21]

Statistical analysis Considering the paucity of similar studies in the literature, the sample size was determined based on SBP effects on EF observed in the previous data from our group[9]: assuming a sample standard deviation of 8% and a correlation coefficient of 0.6 between EF before and after the intervention, 103 patients were needed to identify a 2% difference in EF with a power of 80%.

All data were analyzed using the Statistica PL v.12.0 software (StatSoft, Tulsa, Oklahoma, United States). Categorical variables were reported as percentages, while continuous variables—as means and standard deviations or median and interquartile ranges when data distribution differed from the normal. The χ^2 test was applied for all categorical variables. For continuous variables, the analysis of variance for repeated measures was applied. If the assumptions were not met, a multidimensional approach or the Friedman test was used. For statistically significant results, detailed comparisons using the appropriate post hoc testing (Tukey tests) were conducted. To assess changes in only 2 measurements, the t test for paired samples or the Wilcoxon matched pairs test was used. The results for which the P value was lower than the assumed level of significance $\alpha = 0.05$ ($P < 0.05$) were considered significant.

RESULTS We included 110 patients (age, 23–87 years; 86 men and 24 women), of whom 14 did not complete the study for the following reasons: 2 sudden cardiac deaths; cardiac resynchronization therapy device implantation; 2 hospitalizations (myocardial infarction and limb fracture); alcohol addiction; overnight working; 4 changed the place of residence; 3 withdrew from further participation in the study (health reasons were excluded). Consequently, the trial ended after 96 subjects completed the study (74 in Kraków, 22 in Milan; age, 23–86 years; 74 men and 22 women).

Owing to a specific study design (crossover open trial), in order to verify the probability of a significant carryover effect, we preliminarily assessed the interactions between the intervention sequence (SBT first vs control first) and the observed effects, and found no significant interactions (P value always >0.4). Thus, the results could be safely pooled together.

The clinical characteristics of the patients are shown in TABLE 1, separately for male and female participants. Male participants had slightly higher body mass index and more frequent ischemic

TABLE 1 Baseline characteristics of study participants

Parameter	All participants (n = 96)	Male participants (n = 74)	Female participants (n = 22)	P value
age, y	64.5 (57.0–71.5)	64.5 (57.0–72.0)	64.5 (56.0–69.0)	NS
BMI, kg/m²	26.4 (24.4–29.1)	26.9 (24.4–30.1)	25.0 (21.8–27.1)	0.036
NYHA class I–III, n	11/65/20	7/49/16	4/14/4	NS
EF, %	31.0 (25.0–37.0)	30.0 (25.0–36.0)	32.5 (27.0–38.0)	NS
sPAP, mmHg	35.0 (30.0–44.5)	35.0 (30.0–45.0)	32.5 (30.0–44.0)	NS
office SBP, mmHg	131.0 (118.0–140.0)	131.5 (118.5–140.3)	126.0 (112.0–138.0)	NS
office DBP, mmHg	80.8 (72.0–87.0)	81.0 (74.3–87.3)	79.0 (68.5–85.0)	NS
6MWT distance, m	440.0 (360.0–521.0)	459.0 (380.0–525.0)	410.0 (324.0–462.0)	NS
AHI, 1/h	6.6 (2.6–14.2)	10.0 (3.0–16.0)	4.9 (1.0–6.6)	0.001
central AHI	0.1 (0.0–0.7)	0.1 (0.0–1.0)	0.0 (0.0–0.1)	0.048
obstructive AHI	2.0 (0.4–4.3)	2.3 (0.5–6.0)	1.0 (0.3–2.3)	0.038
ischemic etiology, n (%)	67 (69.1)	56 (75.7)	11 (50)	0.021
β-blockers, n (%)	88 (91.7)	67 (90.5)	21 (95.5)	NS
ACEI/ARB, n (%)	69 (71.9)	54 (73.0)	15 (68.2)	NS
diuretics, n (%)	69 (71.9)	52 (70.3)	17 (77.3)	NS

Data are presented as median (interquartile range) unless stated otherwise.

Abbreviations: 6MWT, 6-minute walk test; ACEI, angiotensin-converting enzyme inhibitor; AHI, apnea–hypopnea index; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; EF, ejection fraction; NYHA, New York Heart Association; NS, nonsignificant; SBP, systolic blood pressure; sPAP, systolic pulmonary artery pressure

etiology and sleep apneas, both central and obstructive. Of 96 patients, 20 had mild to moderate obstructive sleep apnea and 6 had mild to moderate central sleep apnea. On the other hand, there were no significant differences in baseline characteristics according to the intervention sequence (initial SBT versus initial control period).

The main clinical variables before and after the period of SBT are presented in TABLE 2. We observed a significant reduction in global AHI (from 5.6 [2.1–12.8] to 5.35 [2.0–10.8], $P = 0.043$), and a trend for a reduction in central apneas in the whole population ($P = 0.16$); central apneas were significantly reduced in men ($P = 0.039$) (even if the median values were close to 0 due to highly skewed distribution) but not in women ($P = 0.21$). No significant changes in obstructive apneas were observed (TABLE 2).

There was a significant improvement in LVEF after SBT (31.3% ±7.3% vs 32.3% ±7.7%; $P = 0.030$), accompanied by a reduction in end--diastolic diameter of the left ventricle and a trend for a reduction in the E/A ratio, while no change was observed in systolic pulmonary artery pressure (sPAP). The increase in LVEF was more evident in women (from 32.8% to 35.3%) than in men (from 30.8% to 31.4%; P for interaction = 0.07), and in patients with NYHA class I (from 34.4% to 37.6%) compared with those with classes II (from 31.1% to 32.5%) and III (from 30.2% to 28.9%; P for interaction = 0.018), while no effect of CHF etiology was observed (TABLE 2).

The 6MWT distance increased after SBT (449.9 ±122.7 m vs 468.3 ±121.9 m; P <0.001; TABLE 2), regardless of the intervention sequence (FIGURE 2).

During the study, no patient reported safety issues related to study procedures and no adverse events attributable to the intervention occurred.

DISCUSSION Our study attempted to assess a number of clinically relevant parameters in a relatively large sample of patients with CHF before and after SBT. We indeed confirmed previous findings showing that SBT may improve cardiac function and functional performance. Furthermore, our study investigated for the first time the effects of SBT on sleep-disordered breathing in these patients.

Previous studies have suggested that slow breathing or SBT may be a useful adjunct to standard CHF treatment. Acute effects of slow breathing in patients with heart failure were assessed by Bernardi et al,[10] who reported an increase in blood oxygenation levels and improved exercise performance in participants who underwent 1-month training. Improvement in blood oxygenation seems to be related to an improved respiratory mechanics with increased alveolar ventilation[10] as shown also by a study in subjects exposed to hypoxia.[22]

The information on the beneficial effects of SBT was further extended by a pilot study by Parati et al,[9] in which SBT was performed with the same device as was used in the present study. These effects included reductions in both the NYHA class and sPAP, as well as improvement in EF, ventilatory parameters, and quality of life.

Furthermore, Ekman et al[11] found an improvement in NYHA class and breathlessness after 1 month of SBT with the RESPeRATE device.

TABLE 2 Key clinical variables before and after slow breathing training

Parameter	All participants (n = 96)			Male participants (n = 74)			Female participants (n = 22)		
	before SBT	after SBT	P value	before SBT	after SBT	P value	before SBT	after SBT	P value
6MWT, m	449.9 ±122.7	468.3 ±121.9	<0.001	461 (389–529)	480 (402–574)	<0.001	420 ±134	427 ±135	NS
sleep parameters									
AHI, 1/h	5.6 (2.1–12.8)	5.4 (2.0–10.8)	0.043	7.2 (2.6–15.6)	6.5 (2.5–12.4)	0.013	4.0 ±4.3	4.8 ±4.8	NS
AI central	0.0 (0.0–0.7)	0.0 (0.0–0.6)	NS	0.1 (0.0–1.1)	0.1 (0.0–0.7)	0.039	0.0 (0.0–0.1)	0.0 (0.0–0.4)	NS
AI obstructive	1.6 (0.4–4.1)	1.4 (0.5–4.6)	NS	1.8 (0.5–5.3)	1.6 (0.4–5.2)	NS	1.2 ±1.6	1.9 ±2.1	NS
echocardiography									
LVEDd, mm	61 (56–65)	60 (56–66)	0.023	62 (58–66)	61 (57–67)	0.041	57 ±7	57 ±7	NS
LVESd, mm	49 (43–54)	49 (43–55)	NS	50 (44–54)	50 (44–56)	NS	45 (39–52)	43 (40–47)	NS
E/A ratio	0.80 (0.65–1.44)	0.77 (0.67–1.20)	0.061	0.79 (6.4–1.45)	0.77 (0.63–1.22)	NS	1.08 ±0.56	0.95 ±0.40	NS
sPAP, mmHg	35 (29–43)	35 (28–40)	NS	35 (27–43)	35 (27–40)	NS	33 (30–38)	31 (30–43)	NS
LVEF,%	31 ±7	32 ±8	0.030	31 ±7	31 ±7	NS	33 (26–38)	35 (32–40)	0.005

Data are presented as mean ± SD or median (interquartile range) as appropriate.

Abbreviations: AI, apnea index; E/A, early-to-late ventricular filling velocity ratio; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESd, left ventricular end-systolic diameter; SBT, slow breathing training; others, see **TABLE 1**

FIGURE 2 Changes in the 6-minute walk test (6MWT) distance between study phases and treatment sequences; group I, started with slow breathing training; group II, started with standard care; data presented as mean ± standard error
a significant differences
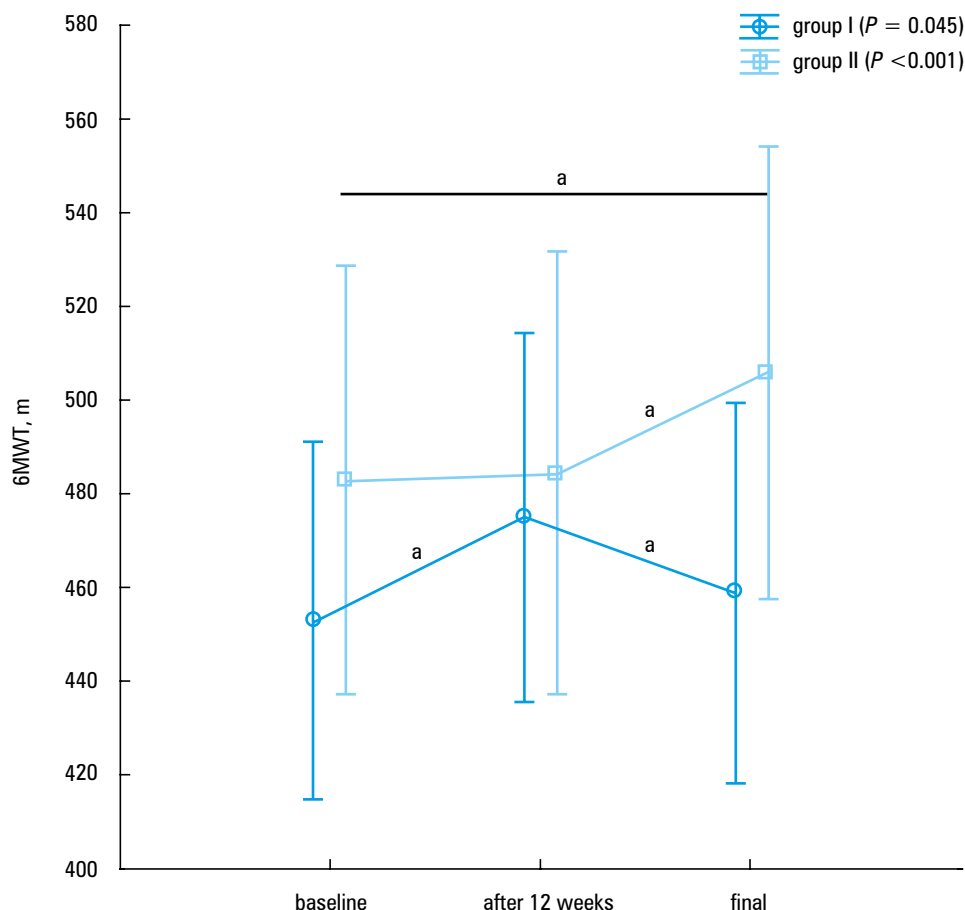
In our study, we demonstrated that SBT led to a significant increase in LVEF in patients with CHF. This improvement might be the result of increasing the sensitivity of baroreceptor reflex and respiratory mechanics itself,[9] with a possible effect on respiratory muscles.[23] Our results are consistent with the results of the study by Parati et al,[9] although in the current study the increase in LVEF was less pronounced (Parati et al[9] reported an increase in LVEF from 32% ±6% to

39% ±9%). Similarly, in our population, we did not show a positive effect of SBT on the reduction of sPAP. These results differ from the results of the pilot study, where sPAP decreased from 49 ±17 mmHg to 38 ±9 mmHg after 10 weeks of SBT.

These discrepancies could be explained by the fact that the pilot study included patients with significantly higher baseline sPAP values: the baseline condition of more severely impaired pulmonary hemodynamics could have amplified a potentially favorable effect of slow breathing, less evident in the current study.[9] On the other hand, the controlled design of our study might also have reduced the foreseeable bias of a small uncontrolled study. Indeed, our data are in agreement with the results of a study by Fox et al[24] in patients with pulmonary hypertension, in whom 6 weeks of exercise training led to a significant improvement in the 6MWT distance despite nonsignificant changes in echocardiography parameters such as stroke volume and sPAP. Interestingly, the benefits in terms of LVEF improvement were mostly evident in female participants and in those with clinically milder CHF. Sex differences in response to exercise training in patients with CHF were previously reported by Pina et al,[25] who found greater benefits (measured by peak oxygen consumption and 6MWT) in women than in men with CHF. Although in our sample there was no significant difference between men and women in terms of a change in the 6MWT distance, the finding of improved LV function after SBT restricted to female sex may further support the usefulness of rehabilitation techniques in this group.

Sleep-disordered breathing is commonly seen in systolic and diastolic heart failure. Sleep apnea comprises several forms of sleep-disordered breathing. Although the pathophysiology of centrally driven apneas differs considerably compared with that of obstructive sleep apnea, they share multiple consequences. The differential diagnosis of the 2 forms of sleep apnea is based on polysomnographic studies where the presence or absence of respiratory movements distinguishes obstructive from central episodes. Apparently, there is a dose-dependent relationship between sleep disorders and the severity of heart failure, with a gradual increase in central sleep apnea occurrence along with the progression of cardiac failure.[14]

In our study, the AHI score equaled 6.6 (interquartile range, 2.6–14.2) at baseline. Nevertheless, the use of SBT resulted in an overall improvement in breathing stability during sleep as the AHI modestly decreased after active treatment (TABLE 2).

We observed a trend towards a reduced number of central apneas and hypopneas (P = 0.16), whereas no change was observed in obstructive episodes. Arguably, the absolute benefit in terms of improvement in sleep-disordered breathing was modest (the median central apnea index values equal to 0 derived from a highly skewed distribution of this variable with numerous participants

having no central apneas). This was probably due to the fact that our intervention was not specifically aimed at reducing the burden of sleep apnea but rather at assessing clinical effects of SBT in a representative group of CHF patients followed in rehabilitation programs. Therefore, study participants had on average relatively mild CHF with good functional performance (79% of patients were classified as NYHA class II or lower), were in stable conditions, and had only modestly elevated body mass index (median, 26.4 kg/m²). Therefore, since the prevalence of both central and obstructive sleep apneas was low, the conceivable benefits of SBT were limited. Also in this case we observed a difference between sexes; however, contrary to what was observed for the changes in LVEF, an improvement in central apneas was only evident in male participants, possibly due to a higher central apnea index at baseline.

The finding of the higher rate of central apneas in men is in line with an increase in the prevalence of central apneas in patients with CHF[26] and in healthy subjects exposed to high altitude where central apneas are common.[27] As a consequence of our findings, we believe that a study including specifically a sample of patients with CHF and sleep-disordered breathing would be justified. Considering that an optimization of heart failure treatment may alleviate central sleep apnea,[28,29] and in the wake of recent controversies regarding whether or not central sleep apnea should be specifically targeted in heart failure patients, a new therapeutic option targeting the pathophysiological basis of central apneas might be of particular interest.

In our previous analyses, we did not show significant changes in blood pressure values after SBT.[8] The RESPeRATE device has been successfully used to lower blood pressure in patients with hypertension. The lack of significant changes in blood pressure values in the studied group could be attributed to low prevalence of elevated blood pressure.

Our data showed an improvement in exercise capacity in the 6MWT after SBT. According to current guidelines, the 6MWT is easy to administer and provides strong indications for measuring the response to medical intervention in patients with heart failure.[21] In ambulatory patients with systolic heart failure, 6MWT provides prognostic utility comparable to that of cardiopulmonary exercise tests, which is the gold standard for the assessment of exercise capacity in this group of patients.[30]

The improvement in physical capacity on the basis of the bicycle cardiopulmonary exercise test in patients with heart failure treated with monthly respiratory training was reported by Bernardi et al.[10] After 1 month of respiratory muscle training, Mancini et al[31] found an improvement in exercise capacity based on the results of the 6MWT. Thus far, only the pilot study by Parati et al, which had similar duration and the same protocol as our study with the use of

the RESPeRATE device, showed an improvement in exercise capacity based on the bicycle cardiopulmonary test.[9] The meta-analysis by Montemezzo et al[32] of all studies on the use of respiratory rehabilitation in patients with heart failure confirms its beneficial effects on physical performance and usefulness in clinical practice, although it should be emphasized that the number of these studies is low.

Our study has several strengths. First, the respiratory profile after SBT with RESPeRATE had never been tested previously; second, the sample size was larger than in most previous studies[9,11]; third, the controlled design and the use of a device designed for SBT (and approved by the Food & Drug Administration for blood pressure lowering) followed a standardized exercise protocol. Furthermore, this device implements a series of features that make the exercise easier for the patient, including the individualized acoustic guidance of breathing frequency, which results in its gradual reduction, and visual feedback on the exercise performance. This is important as self-maintenance of a constant number of breaths by the patient is a difficult task, and rigid breathing pacing could have a negative effect on exercise performance.

There are also a few limitations. First, the majority of enrolled patients were in NYHA class II, thus the information on the tolerability and efficacy in more severe CHF is limited. Second, since for practical reasons we implemented a crossover rather than a parallel-group design, there might have been a carryover effect; however, the lack of interaction of the intervention sequence with the observed changes suggests that such an effect was not relevant. Third, a strict supervision of exercise quality in patients' homes was not performed, and the observed effect might have been diluted by participants who were not compliant with the training. Fourth, we did not assess breathing pattern during daytime and therefore have no data on the presence of central apneas in the awake period.[33] Finally, we could not exclude the possible influence of comorbidities (eg, diabetes, hypertension) or drugs on the results, although pharmacotherapy was kept stable during the study.

In conclusion, in patients with stable chronic systolic heart failure, SBT improved physical capacity and systolic left ventricular function, with a tendency to attenuate sleep disturbances, mainly central apnea. The latter results support the hypothesis that central sleep apnea may represent a consequence of heart failure or an adaptation mechanism to the complex neurohormonal abnormalities observed in these patients. We believe that device-guided SBT may be successfully implemented as a home-based rehabilitation tool in patients with CHF, leading to improvements in their clinical status and breathing patterns.

Contribution statement KS conceived the idea for the study. KS, DC, KK-J, and GP contributed to the design of the research. TD, DD-D, GK, KS, CL, AB, and SS were involved in data collection. GB, TD, and GK analyzed the data. KS and KK-J coordinated funding for the project. All authors edited and approved the final version of the manuscript.

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