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The Effects of Game-Based Breathing Exercise on Pulmonary Function in Stroke Patients: A Preliminary Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Reduction of respiratory function along with hemiparesis leads to decreased endurance, dyspnea, and increased sedentary behavior, as well as to an increased risk of stroke. The main purpose of this study was to investigate the preliminary effects of game-based breathing exercise (GBE) on pulmonary function in stroke patients.

Material/Methods: Thirty-eight in-patients with stroke (22 men, 16 women) were recruited for the study. Participants were randomly allocated into 2 groups: patients assigned to the GBE group (n=19), and the control group (n=19). The GBE group participated in a GBE program for 25 minutes a day, 3 days a week, during a 5 week period. For the same period, both groups participated in a conventional stroke rehabilitation program. Forced vital capacity (FVC), forced expiratory volume at 1 second (FEV_1), FEV_1/FVC, and maximum voluntary ventilation (MVV) were measured by a spirometer in pre- and post-testing.

Results: The GBE group had significantly improved FVC, $FEV_{1,}$ and MVV values compared with the control group ($p<0.05$), although there was no significant difference in FEV_1/FVC value between groups. Significant short-term effects of the GBE program on pulmonary function in stroke patients were recorded in this study.

Conclusions: These findings gave some indications that it may be feasible to include GBE in rehabilitation interventions with this population.

MeSH Keywords: **Breathing Exercises • Feedback, Sensory • Respiratory Function Tests • Stroke**

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Background

Stroke survivors often have poor lung function, which has been found to be approximately 50% below that of age- and sex-adjusted norms [1,2]. Reduction of respiratory function along with hemiparesis leads not only to decreased endurance, dyspnea, and increased sedentary behavior, but also to an increased risk of stroke [3]. This reduction of respiratory function can also cause aspiration, which can develop into pneumonia and a worsening of the patient's condition [4,5]. Mortality in stroke patients has been shown a 6-fold increase due to pneumonia [6,7]. In addition, low respiratory muscle strength is one of the main reasons for pulmonary and respiratory dysfunction after stroke. Decreased strength of lower abdominal muscles during the respiratory cycle is also noted in stroke patients, and this low respiratory muscle function decreases the effectiveness of rehabilitation in stroke patients because of exercise intolerance [8]. Low respiratory muscle strength is an independent risk factor for cardiovascular disease and has been suggested to lead to an increased risk of stroke [3]. Therefore, stroke patients require specific training to improve respiratory muscle strength and pulmonary function.

Respiratory muscle training (RMT), in which resistance is provided to respiratory muscles during breathing, has been used to improve respiratory function [9–11]. Previous studies on inspiratory muscle training reported that it improved the patient's capacity to perform activities of daily living and exercises [12]. In addition to these, respiratory muscle training positively affects quality of life [13,14]. Most previous studies on RMT has also been used to increase strength and therefore improve respiratory function in patients with cardiac disease [15] and chronic obstructive pulmonary disease [16,17]. However, there are very few studies on respiratory training in stroke patients [9]. Moreover, resistance in majority of these respiratory muscle studies for stroke patients was provided only by means of equipment.

Biofeedback is an effective treatment technique for patients with upper and lower limb motor deficiency due to neurological injury. It is used for facilitating normal movement patterns in post-stroke rehabilitation. Traditionally, biofeedback provides information through visual images and auditory feedback. Recently, it has been used in conjunction with game-based exercises or virtual reality, which has given patients a chance to undergo rehabilitation through activities that are of interest to them or are based on daily living activities [18–20].

It is barely found the research of biofeedback in the field of breathing exercise for stroke patients as a new intervention. Hence, the aim of this study was to evaluate the preliminary effects of game-based breathing exercise providing biofeedback on pulmonary function in stroke patients.

Material and Methods

Subjects

All individuals with a diagnosis of stroke admitted to an inpatient rehabilitation ward at the 'B' rehabilitation hospital (Gyeonggi Province, South Korea) were eligible after meeting the following inclusion criteria: (1) history of a stroke at least 6 months before the study; (2) able to understand and follow simple verbal instructions; (3) a Mini-mental State Examination-Korean (MMSE-K) score of >24 [21]; (4) no facial palsy and unrestricted movement of the lips; (5) a forced expiratory volume in one second (FEV_1) under 93% of the predicted normal value [22]; (6) no orthopedic, neurologic, or unstable cardiac conditions; (7) no receptive aphasia and no history of thoracic or abdominal surgery; and (8) voluntary participation and the ability to communicate effectively. Exclusion criteria were as follows: (1) history of cardiac and/or chronic pulmonary disease; (2) clinical signs of cardiac and/or pulmonary disease; (3) presence of a severe visual disability and visual field defects; (4) inability to perform the tests; and (5) use of medications that could cause dizziness; (6) The participants receiving any cardiopulmonary fitness training that could have affected the study. Thirty eight participants were enrolled in the trial. Two research assistants and a physical therapist who worked in the rehabilitation hospital participated in the intervention and measurement session. All protocols and procedures were approved by the Institutional Review Board of Sahmyook University, and all subjects signed a statement of informed consent.

Procedure

This study designed as a randomized, controlled trial. After pretesting, 38 participants were randomized to an experimental (n=19) and control group (n=19). The randomization process was performed using random allocation software [23]. The experimental and control groups both participated in conventional stroke rehabilitation program, but only the experimental group participated in game-based breathing exercise (Figure 1). Conventional stroke rehabilitation program consisted of joint mobility, eccentric contraction, muscle strengthening and walking exercise for 30 minutes once a day, 5 days a week, over 5 weeks [24].

The breathing trainer (Breathing+ package, Breathing Labs, Slovenia) was provided for this study. It consists of a game application that was downloaded to a laptop as well as a headset. Once the game application is started, the sensor in the headset recognizes the patient's respiration, which initiates the game, depending on the respiratory pressure and the rhythm of the respiratory cycle. This game application includes 14 different games including blowing a balloon, flying a kite, an airplane, and a windmill, etc. Each game has a total of 10 sets and provides

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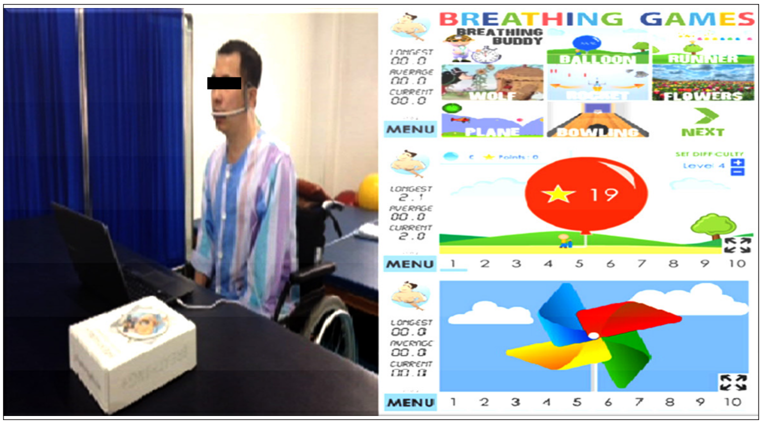

Figure 1. Game-based breathing exercise.

the inhalation period, the longest exhalation period, and their average value in real time. The patients' game preferences were taken into consideration, and the patients were allowed to select a specific screen of their choice. To avoid falls, the games were played with the patients seated in an armchair (although not leaning on the back of the chair). In the event that patients felt dizzy or seemed to lose control, a break time was given until normal rhythm and control was regained. The research assistants provided the patients with the instructions, and encouraged the patient to perform the tests, and also demonstrated the game and monitored the patients from the beginning till the end of the game. For a more effective breathing exercise, patients were asked to perform longer exhalations, and the game scores were recorded. Visual feedback of the score motivated the patients to increase their training load. The total duration of the game-based breathing exercises was 25 minutes; breathing control exercise for relaxation was performed for 5 minutes at the beginning and end of this period.

Patients in the GBE group received 25 minutes of daily game-based breathing exercises, 3 days/week for 5 weeks. During the training period, all patients of both groups participated in a daily conventional rehabilitation program consisting of mat exercises and balance and gait training, for 30 minutes, 5 days/week, conducted by physical therapists employed at the hospital. After 5 weeks of training, all participants underwent the same pulmonary function tests with a spirometer, the same as at the start of the study.

Measurements

A spirometer (SP-1, Schiller, USA) was used for the measurement of pulmonary function. The variables tested were FVC, FEV_1, and FEV_1/FVC. FVC is a pivotal indicator of restrictive ventilation disorder. Generally, the patient is asked to take the deepest breath they can, and then exhale into the sensor as hard as possible, for as long as possible, preferably at least 6 seconds. During the test, soft nose clips may be used to prevent air escaping through the nose. The test is repeated 3 times to record their average measures. FEV_1 is defined as the maximum exhaling capacity measured in 1 second; it is the most useful indicator because it requires willingness of the patient. In an obstructive disorder, the respiratory tract closes faster than normal and the corresponding FEV_1 decreases markedly. However, as FVC also might be decreased in an obstructive disorder, we need to analyze and compare the ratio of FEV_1 to FVC. Generally, when the ratio is > 70%, it is regarded as restrictive, while it is considered as obstructive if it is <70%. MVV is widely known as the functional variable for the pulmonary function test. It is a measure of the maximum amount of air that can be inhaled and exhaled within 1 minute. For the comfort of the patient, this is done over a 15-second time period before being extrapolated to a value for 1 minute expressed as liters/minute. The test is useful in diagnosing respiratory disorders caused by other neurological diseases or musculoskeletal disorders.

Statistical analysis

All statistical analyses were performed using SPSS version 19.0 statistical software for Window (SPSS Inc., Chicago, IL, USA). Results are presented as mean ± standard deviation. Prior to training, the normality of the data was assessed with the 1-sample Shapiro-Wilk test.

Results of chi-square analysis and the independent samples t-test were calculated to examine differences for all outcome variables. The paired t-test was used to compare pulmonary function before and after treatment. The independent samples t-test was performed to identify differences between groups. For all tests, statistical significance level was set at 0.05.

Results

No significant differences existed in baseline values between the general characteristics or dependent variables of the 2 groups (Tables 1, 2)

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Table 1. Baseline characteristics of subject.

	GBE group (n=19)	Control group (n=19)	χ^2/t(p)	
Gender (male/female)	19 (12/7)	19 (10/9)	0.432	(0.806)
Age (year)	55.05±10.87	56.73±9.59	-.506	(0.616)
Height (cm)	162.63±7.81	163.05±9.18	-.152	(0.880)
Weight (kg)	64.51±6.28	63.88±11.61	0.207	(0.837)
FEV_1% pred	75.00±21.84	67.74±27.66	0.850	(0.401)
BMI (kg/m^2)	24.69±3.16	23.87±3.00	0.815	(0.420)

BMI – body mass index; FEV_1% pred – the predicted percentage of forced expiratory volume in 1 second; GBE – game-based breathing exercise.

Table 2. Pre-and post-training lung volumes.

Variables	EG (n=19)			CG (n=19)		
	Pre	Post	Post-pre	Pre	Post	Post-pre
FVC(L)	2.50 (0.82)	3.15 (0.78)*	−0.65 (0.86)**	2.58 (1.11)	2.34 (0.96)	0.24 (0.53)
FEV_1(L)	1.90 (0.55)	2.43 (0.68)*	−0.53 (0.78)**	1.75 (0.83)	1.80 (0.70)	−0.04 (0.56)
FEV_1/FVC (%)	77.08 (15.96)	77.79 (12.26)	−0.72 (14.72)	71.71 (21.36)	79.59 (13.32)	−7.88 (19.63)
MVV (L/min)	51.36 (18.73)	66.56 (23.76)*	−15.20 (22.23)**	53.71 (29.33)	49.15 (27.21)	4.55 (19.06)

EG – experimental group; CG – control group; FVC – forced vital capacity; FEV_1 – forced expiratory volume in 1 second;
MVV – maximum voluntary ventilation. * Means significant difference within group; ** means significant difference between groups.

With regard to pulmonary function, after completing the 5-week intervention program, the FVC was significantly improved from 2.50 L to 3.15 L in the experimental group (p=0.001) but was not significantly improved in the control group. The FEV_1 was significantly improved from 1.90 L to 2.43 L in the experimental group (p<0.05) and from 1.75 L to 1.80 L in the control group (p<0.05). In comparing the 2 groups, the degrees of change in the FVC and the FEV_1 were statistically greater in the experimental group than in the control group (p<0.05).

The MVV was significantly improved from 51.36 L/min to 66.56 L/min in the experimental group (p<0.05), whereas the MVV was decreased from 53.71 L/min to 49.15 L/min in the control group (p<0.05). In comparing the 2 groups, the degree of change in the MVV was statistically greater in the experimental group than in the control group (p<0.05).

After the intervention, the value of the FEV_1/FVC within groups increased (77.79±12.26% from 77.08±15.96% in the experimental and 79.59±13.32% from 71.71±21.36% in the control groups). However, there was no significant difference in the value of the FEV_1/FVC between the 2 groups.

Discussion

This study demonstrated that a 5-week program of game-based breathing exercise improves pulmonary function in stroke patients, and was associated with an increase in lung volume and respiratory muscle strength.

MVV is a reflection of the global integrity of the respiratory system as a whole. Thus, MVV decreases with loss of coordination of the respiratory muscles, deformity of the thoracic bellow, neurologic diseases, deconditioning, and ventilatory defects [25]. Generally, resistance muscle training has been used to improve muscle function and the strength of respiratory muscles. Sutbeyaz et al. (2010) found that RMT program had a significant effect on MVV (60.27 L/min to 65.93 L/min) in patients with sub-acute stroke [26]. Britto et al. (2011) found significant effects of an RMT program for inspiratory strength and endurance in chronic stroke survivor [27]. In the present study, game-based breathing exercise significantly improved MVV (51.36 L/min to 66.56 L/min) in the GBE group. The significant increase in MVV in this study suggests that hyperventilation to increase the score during GBE might activate

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and strengthen the respiratory muscles of stroke patients. Therefore, GBE may be a feasible way to improve respiratory muscle strengthening such as by RMT.

It has been found that lower levels of FVC and FEV_1 are associated with an increased risk of stroke in those already at a high risk [28]. Our study showed that the values of FVC and FEV_1 (2.50 to 3.15 L, 1.90 to 2.43 L in the experimental group, respectively) were improved by game-based breathing exercise in stroke patients. The greatest increases occurred in FVC and FEV_1 ($p<0.05$).

The FEV_1/FVC ratio is a calculated ratio used in the diagnosis of obstructive and restrictive lung disease. The values of FEV_1/FVC ratio in stroke are approximately more than 70%. However, stroke patients may have obstructive lung disease due to chronically decreased expansion of the paretic-side thorax [29]. In the present study, both groups presented FEV_1/FVC ratios higher than 70%, although the difference in FEV_1/FVC ratio between groups was not statistically significant.

These important observations suggest that game-based breathing exercise might be able to improve dyspnea, exercise performance, and quality of life. Furthermore, stroke recurrence rate, stroke mortality, and risk of various forms of respiratory muscle weakness may be reduced.

Most of the trained patients reported subjective improvement in aspiration problems during daily activities after the training period. Aspiration can develop into pneumonia, which in turn can lead to a worsening of the patient's condition. Recent studies in patients with respiratory diseases suggest that the magnitude of experienced aspiration is at least partly related to the work performed by the inspiration muscles and their strength [4,5]. Therefore, it is not surprising that we observed improvement in the reported aspiration following the training period in the GBE group.

The conventional breathing exercises such as diaphragmatic breathing, pursed-lip breathing, and air-shifting are often repetitive, causing patients to lose interest and not complete the rehabilitation process. In this study, voluntary hyperventilation with game was used. To our knowledge, this is the first randomized controlled trial of game-based breathing exercise in stroke patients. The use of video games coupled with breathing exercise has numerous advantages compared to conventional breathing exercises applied in the same context. First, our game-based breathing exercise was random and precise; thus, the participants were required to breathe in a timely, goal-directed fashion in each game. Participation in these games therefore requires strong voluntary breathing. Second, our game-based breathing system provided an interactive environment. Meaningful, intensive, enjoyable tasks were related to real-life interests and activities of daily living. Third, imagery, proprioceptive training, and biofeedback techniques such as verbal encouragement and visual feedback are utilized for performance enhancement. The game-based breathing exercise was purposeful and challenging, with the intensity of practice and positive feedback being consistently and systematically manipulated. The main advantage of our gaming system was that complicated and expensive display systems were not required. Significant short-term effects of game-based breathing exercise on pulmonary function were recorded in this study. These effects support game-based breathing exercise as a potential therapeutic resource in stroke rehabilitation.

In this study, spirometry was used to assess pulmonary function in all participants. Pulmonary function tests are volitional tasks that require maximum effort from the participant. Hence, they are likely to be influenced by the participant's motivation, condition, and alertness, as well as their ability to make an airtight seal around the mouthpiece of the measuring device. While our results showed that all participants experienced an increase in lung volume, the long-term effects of game-based breathing exercise in our patients were not monitored. A consensus has been reached regarding the lower effectiveness of exercise programs shorter than 6–8 weeks [30,31]. Therefore, we suggest that the long-term effect of game-based breathing exercise in stroke patients should be determined.

Further research is necessary to conduct a controlled clinical investigation designed to validate the effectiveness of game-based breathing exercise as a tool in rehabilitation. These future studies should focus on: (1) motivating the participants and achieving a greater extent of performance; (2) providing an increased selection of games, which is an important factor in keeping the users motivated and interested; and (3) providing training with a portable device.

Conclusions

The present study evaluated the effects of game-based breathing exercise on pulmonary function in stroke patients. There were significant differences in FVC, FEV_1, and MVV between the GBE and control groups. However, the difference in the extent of change in the FEV_1/FVC value was not statistically significant. These findings suggest that the inclusion of game-based breathing exercise in rehabilitation programs might be beneficial for stroke patients.

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References:

1. Billinger SA, Coughenour E, Mackay-Lyons MJ, Ivey FM: Reduced cardiorespiratory fitness after stroke: biological consequences and exercise-induced adaptations. Stroke Res Treat, 2012; 2012: 959120
2. Mackay-Lyons MJ, Makrides L: Exercise capacity early after stroke. Arch Phys Med Rehabil, 2002; 83: 1697–702
3. Van Der Palen J, Rea TD, Manolio TA et al: Respiratory muscle strength and the risk of incident cardiovascular events. Thorax, 2004; 59: 1063–67
4. Martino R, Foley N, Bhogal S et al: Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. Stroke, 2005; 36: 2756–63
5. Masiero S, Pierobon R, Previato C, Gomiero E: Pneumonia in stroke patients with oropharyngeal dysphagia: a six-month follow-up study. Neurol Sci, 2008; 29: 139–45
6. Vernino S, Brown RD Jr, Sejvar JJ et al: Cause-specific mortality after first cerebral infarction: a population-based study. Stroke, 2003; 34: 1828–32
7. Wilson RD: Mortality and cost of pneumonia after stroke for different risk groups. J Stroke Cerebrovasc Dis, 2012; 21: 61–67
8. Teixeira-Salmela LF, Parreira VF, Britto RR et al: Respiratory pressures and thoracoabdominal motion in community-dwelling chronic stroke survivors. Arch Phys Med Rehabil, 2005; 86: 1974–78
9. Pollock RD, Rafferty GF, Moxham J, Kalra L: Respiratory muscle strength and training in stroke and neurology: a systematic review. Int J Stroke, 2013; 8: 124–30
10. Verges S, Kruttli U, Stahl B et al: Respiratory control, respiratory sensations and cycling endurance after respiratory muscle endurance training. Adv Exp Med Biol, 2008; 605: 239–44
11. Xiao Y, Luo M, Wang J, Luo H: Inspiratory muscle training for the recovery of function after stroke. Cochrane Database Syst Rev, 2012; 5: CD009360
12. Reid WD, Samrai B: Respiratory muscle training for patients with chronic obstructive pulmonary disease. Phys Ther, 1995; 75: 996–1005
13. Dall'ago P, Chiappa GR, Guths H et al: Inspiratory muscle training in patients with heart failure and inspiratory muscle weakness: a randomized trial. J Am Coll Cardiol, 2006; 47: 757–63
14. Scherer TA, Spengler CM, Owassapian D et al: Respiratory muscle endurance training in chronic obstructive pulmonary disease: impact on exercise capacity, dyspnea, and quality of life. Am J Respir Crit Care Med, 2000; 162: 1709–14
15. Stein R, Chiappa GR, Guths H et al: Inspiratory muscle training improves oxygen uptake efficiency slope in patients with chronic heart failure. J Cardiopulm Rehabil Prev, 2009; 29: 392–95
16. Hill K, Jenkins SC, Philippe DL et al: Comparison of incremental and constant load tests of inspiratory muscle endurance in COPD. Eur Respir J, 2007; 30: 479–86
17. Mador MJ, Deniz O, Aggarwal A et al: Effect of respiratory muscle endurance training in patients with COPD undergoing pulmonary rehabilitation. Chest, 2005; 128: 1216–24
18. Teasell R, Meyer MJ, Mcclure A et al: Stroke rehabilitation: an international perspective. Top Stroke Rehabil, 2009; 16: 44–56
19. Onate JA, Guskiewicz KM, Sullivan RJ: Augmented feedback reduces jump landing forces. J Orthop Sports Phys Ther, 2001; 31: 511–17
20. Tate JJ, Milner CE: Real-time kinematic, temporospatial, and kinetic biofeedback during gait retraining in patients: a systematic review. Phys Ther, 2010; 90: 1123–34
21. Folstein MF, Folstein SE, Mchugh PR: "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res, 1975; 12: 189–98
22. Barreiro E, Coronell C, Lavina B et al: Aging, sex differences, and oxidative stress in human respiratory and limb muscles. Free Radic Biol Med, 2006; 41: 797–809
23. Saghaei M: Random allocation software for parallel group randomized trials. BMC Med Res Methodol, 2004; 4: 26
24. Kim J, Park JH, Yim J: Effects of respiratory muscle and endurance training using an individualized training device on the pulmonary function and exercise capacity in stroke patients. Med Sci Monit, 2014; 20: 2543–49
25. Macintyre N: Respiratory care: principles and practice 2011: Jones & Bartlett Learning
26. Sutbeyaz ST, Koseoglu F, Inan L, Coskun O: Respiratory muscle training improves cardiopulmonary function and exercise tolerance in subjects with subacute stroke: a randomized controlled trial. Clin Rehabil, 2010; 24: 240–50
27. Britto RR, Rezende NR, Marinho KC et al: Inspiratory muscular training in chronic stroke survivors: a randomized controlled trial. Arch Phys Med Rehabil, 2011; 92: 184–90
28. Myint PK, Luben RN, Surtees PG et al: Respiratory function and self-reported functional health: EPIC-Norfolk population study. Eur Respir J, 2005; 26: 494–502
29. Enright PL, Kronmal RA, Higgins M et al: Spirometry reference values for women and men 65 to 85 years of age. Cardiovascular health study. Am Rev Respir Dis, 1993; 147: 125–33
30. Sezer N, Ordu NK, Sutbeyaz ST, Koseoglu BF: Cardiopulmonary and metabolic responses to maximum exercise and aerobic capacity in hemiplegic patients. Funct Neurol, 2004; 19: 233–38
31. Troosters T, Casaburi R, Gosselink R, Decramer M: Pulmonary rehabilitation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 2005; 172: 19–38

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