Received: 26 June 2018 | Revised: 2 November 2018 | Accepted: 20 November 2018

DOI: 10.1002/ajmg.a.61016

WILEY AMERICAN JOURNAL OF medical genetics PART A

RESEARCH ARTICLE

Inspiratory muscle strength training improves lung function in patients with the hypermobile Ehlers–Danlos syndrome: A randomized controlled trial

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Funding information
Institut de Recherche Expérimentale et Clinique

As exertional inspiratory dyspnea is a common disabling complaint in hypermobile Ehlers–Danlos syndrome (hEDS) often also known as joint hypermobility syndrome (JHS), we investigated inspiratory muscle (IM) strength in patients with hEDS, and we assessed the effects of IM training (IMT) on IM strength, lung function, and exercise capacity. A prospective evaluation of IM strength followed by a randomized controlled trial of IMT was performed in women with hEDS. Sniff nasal inspiratory pressure (SNIP) was used to routinely measure IM strength and IMT was carried out using a pressure threshold device. IM strength (main outcome), cardiopulmonary function, exercise capacity, and emotional distress of both the treated and control groups were evaluated at the start and at the end of the 6-week training period. IM strength was reduced (<80% of predicted) in 77% of patients (80/104). Lung function was normal, although 24% of patients had a higher forced expiratory vital capacity (FVC) than normal and 12% of patients had a higher total lung capacity (TLC) than normal. Both the IMT and control groups (n = 20) had similar baseline characteristics. Significant changes were noted only in the IMT group after IMT. At the end of the program, IMT improved SNIP (20%) (before: 41 $\pm$ 17 cm H_2O [28, 53] vs. after: 49 $\pm$ 18 cm H_2O [34;65]), six-minute walking distance (6MWD) (60 m) (455 $\pm$ 107 m [379,532] vs. 515 $\pm$ 127 m [408, 621]), and forced expiratory volume in one second (FEV1) (285 mL) (94 $\pm$ 14% pred [84,104] vs. 103 $\pm$ 11% pred [94, 112]). IM strength is significantly reduced in patients with hEDS. IMT improved IM strength, lung function, and exercise capacity. Our findings suggest that IMT should be added to usual care.

Key messages

What is the key question?: Are inspiratory muscle strength and lung function normal in Ehlers–Danlos syndrome hypermobility type (EDS-HT) patients? Can inspiratory muscle training be a potential therapy to improve inspiratory muscle strength, lung function, functional exercise performance, anxiety, and depression?

What is the bottom line?: IM strength was significantly reduced in patients with hEDS, but it was improved by inspiratory muscle training similarly to lung function and exercise capacity.

Why read on?: This is the first description of inspiratory muscle strength and lung function in hEDS and the first trial investigating the effect of inspiratory muscle training in hEDS.

KEYWORDS

connective tissue disease associated lung disease, exercise, lung physiology

Abbreviations: bpm, beats per minute; COPD, chronic obstructive pulmonary disease; EDS, Ehlers–Danlos syndrome; FEV1, forced expiratory volume in one second; FVC, forced expiratory vital capacity; HADS, Hospital Anxiety and Depression Scale; -HT, -hypermobility type; IMT, inspiratory muscle training; JHS, joint hypermobility syndrome; MCID, minimal clinically important difference; SNIP, sniff nasal inspiratory pressure; SpO2, pulsed oxygen saturation; TLC, total lung capacity; 6MWT, six-minute walk test.

1 | INTRODUCTION

Ehlers–Danlos syndrome (EDS) comprises a group of inherited connective tissue disorders that affect many body systems (gastrointestinal, cardiovascular, skeletal, etc.) (Byers & Murray, 2014) and it is the commonest form of joint hypermobility. The 2017 international classification recognizes 13 clinical subtypes of EDS with mutations in 19 genes (Malfait et al., 2017). A distinction is now made between hEDS, isolated, nonsyndromic joint hypermobility, and hypermobility spectrum disorders. They are the most common phenotypes of EDS. The last two phenotypes may be transitory contrarily to hEDS (Castori et al., 2017; Castori & Hakim, 2017). The hypermobile Ehlers–Danlos syndrome (hEDS) is still a clinical diagnosis without known associated genes (Grahame, 2013). Only patients with a more systemic phenotype and/or families with clear Mendelian transmission can be categorized as hEDS. People with this chronic and disabling condition have loose, unstable, and chronically painful joints. They also have easily bruised skin, extreme tiredness, cardiovascular autonomic dysfunction, gastrointestinal dysmotility as well as neurological and spinal dysfunction (Malfait et al., 2017).

The prevalence of hEDS is estimated to be more than 2% in Caucasians (Fikree, Aziz, & Grahame, 2013). The patients with hEDS may present with tendinopathies, joint dislocation or subluxation, arthralgia, widespread pain or early onset osteoarthritis (Fikree et al., 2013). Other clinical manifestations include cardiovascular pathology, dysautonomia (Bravo & Wolff, 2006), chronic fatigue (Voermans et al., 2010), gastrointestinal dysmotility (Zeitoun et al., 2013), and proprioceptive deficits (Clayton, Jones, & Henriques, 2015). Because of lack of awareness, heterogeneity of clinical presentation, and reliance on physical examination for diagnosis, hEDS in patients was often overlooked, misdiagnosed, and mistreated (Grahame, 2013; Kumar & Lenert, 2017).

Many patients with hEDS (up to 50%) describe exertional dyspnea and breathing difficulties. Chest wall deformities, airway collapse, vocal cord abnormalities, and some swallowing difficulties have been reported (Ayres, Pope, Reidy, & Clark, 1985; Castori, Camerota, Celletti, Danese, et al., 2010; Hunter, Morgan, & Bird, 1998), but lung function has been poorly investigated in patients with hEDS. In a study conducted in adults with EDS, pulmonary CT scans were essentially normal despite physiological abnormalities and the authors suggested that it could be related to the underlying connective tissue defects and altered mechanical properties of the lungs (Morgan, Pearson, Davies, Gooi, & Bird, 2007).

Respiratory complications in patients with hEDS could also be due to muscle weakness. The severe muscle dysfunction detected in the lower extremities (Rombaut et al., 2012) may also affect the respiratory muscles and cause shortness of breath. To date, no study has examined inspiratory muscle (IM) strength in patients with hEDS. Respiratory muscle weakness has been correlated with dyspnea and fatigue in patients with various diseases such as multiple sclerosis or heart failure (Bosnak-Guclu et al., 2011; Lee & Holland, 2014; Ray, Mahoney, & Fisher, 2015). Inspiratory muscle training (IMT) increased functional capacity and perception of well-being in patients with diverse conditions such as chronic obstructive pulmonary disease (COPD) (Nikoletou et al., 2016), heart failure(Bosnak-Guclu et al., 2011), multiple sclerosis(Gosselink, Kovacs, Ketelaer, Carton, & Decramer, 2000), and in recipients of allogenic hematopoietic stem cell transplantation (Bargi, Guclu, Aribas, Aki, & Sucak, 2015).

In this study, IM strength and lung function were prospectively evaluated in patients with hEDS and IMT was investigated as a potential therapy to improve IM strength (main outcome), lung function, functional exercise performance, anxiety, and depression (secondary outcomes) in a randomized controlled trial.

2 | MATERIALS AND METHODS

2.1 | Patient information

We prospectively assessed all individuals who were referred in July and August 2015 to the rheumatology outpatient ward of Cliniques universitaires Saint-Luc (Brussels, Belgium) and were suspected to have a heritable connective tissue disorder. The diagnosis was established when patients met both the Villefranche and Brighton inclusion criteria for hEDS (Beighton, De, Steinmann, Tsipouras, & Wenstrup, 1998). Patients who were smokers or who had other connective tissue or muscle disorders, developmental delay, respiratory comorbidities, or airway infections in the last 4 weeks were excluded. As more than 90% of patients with hEDS are female (Castori, Camerota, Celletti, Grammatico, & Padua, 2010), males were also excluded from the study. The patients initially selected according to the above criteria were subsequently reviewed according to the 2017 classification and only the patients also meeting the 2017 criteria were selected for data management and interpretation (Malfait et al., 2017).

All enrolled subjects had a Beighton's score over 5/9, a history of infancy/childhood joint hypermobility, easy bruising, soft/velvety skin, and other clinical signs. A skin biopsy was systematically performed to identify anomalies in the collagen network of the dermis, not for diagnostic purposes but for experimental purpose strictly linked to the project. Thus, non-sun-exposed skin specimens (inner part of the arm or upper portion of the thigh) were sampled in all patients, and the dermis was examined under a Zeiss EM910 electron microscope operated at 60 kV (Hermanns-Le et al., 2012).

All included patients had defects in dermal collagen with small flower-like collagen fibers in the papillary or reticular dermis, variable collagen fiber diameters, and irregular interfiber spacing. Although each one of these three primary morphologic abnormalities can be observed alone in disorders not related to EDS, the three are present together in all patients with typical hEDS as well as in members of their family who have a low Beighton score (Hermanns-Le et al., 2012). Also, 15% of patients had twisted collagen fibers and 45% had granulofilamentous deposits inside the collagen bundle. Elastic fibers were regular in 40% of patients and had frayed contours in the remaining 60%.

All patients signed a written informed consent form according to the Declaration of Helsinki and the current guidelines for Clinical Good Practice after approval by the Institutional Medical Ethics Committee (B403201525660). The study was registered (NCT02646215). This study was approved by the Institutional Medical Ethics Committee and informed consent was given by all participants.

2.2 | Study design

The study was divided into two parts. In the first part of the study, the lung function and IM strength of the subjects were assessed prospectively during a routine outpatient visit.

In the second part, a randomized controlled trial was conducted according to the Consolidated Standards of Reporting Trials protocol (Figure 1). When reduced IM strength (<80% of the predicted values) was detected by the physician during the first part of the study, patients were eligible for the second part of the study. From this sample of patients, the consecutive patients who gave their consent (only criteria for eligibility) until the required sample size was achieved (n = 20) were assessed for functional exercise performance, anxiety, depression, and physical activity. These patients were randomized by a computer-generated random number list (www.randomizer.org) with an allocation ratio of 1:1 into two groups (IMT and control).

The IMT group performed five unsupervised sessions of IMT per week for 6 weeks. While wearing a nose clip and being comfortably seated, patients were asked to inspire through the Threshold IMT (Philips-Respironics, Murrysville, PA). Each session included six series of 10 repetitions with progressively increasing resistance ranging from 60% to 85% of the initial maximal sniff nasal inspiratory pressure (SNIP). The group allocation was concealed, and the assessment was blinded. Patients in both groups were assessed at the start and end of the 6-week training period. Patients in the IMT group kept a daily diary for monitoring their adherence to the IMT protocol.

2.3 | IM strength

The maximal SNIP was used to assess IM strength (Stefanutti, Benoist, Scheinmann, Chaussain, & Fitting, 2000) following the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines (ATS/ERS, 2002) using a hand-held pressure meter (Micro RPM, Care Fusion, Kent, United Kingdom). Subjects were asked to perform 20 sniff ma

neuvers with maximal inspiratory effort. The highest result was recorded and expressed in absolute and predicted values (Uldry & Fitting, 1995) and by calculating the improvement adjusted for baseline. To ensure data reliability, the same experienced staff member conducted all SNIP tests.

2.4 | Spirometry

Spirometry was performed using the Masterscreen spirometer (Jaeger, Würsburg, Germany) according to the ATS/ERS guidelines (Miller et al., 2005). The reference equations established by the Global Lung Function Initiative were used. The differences between initial and final values were calculated.

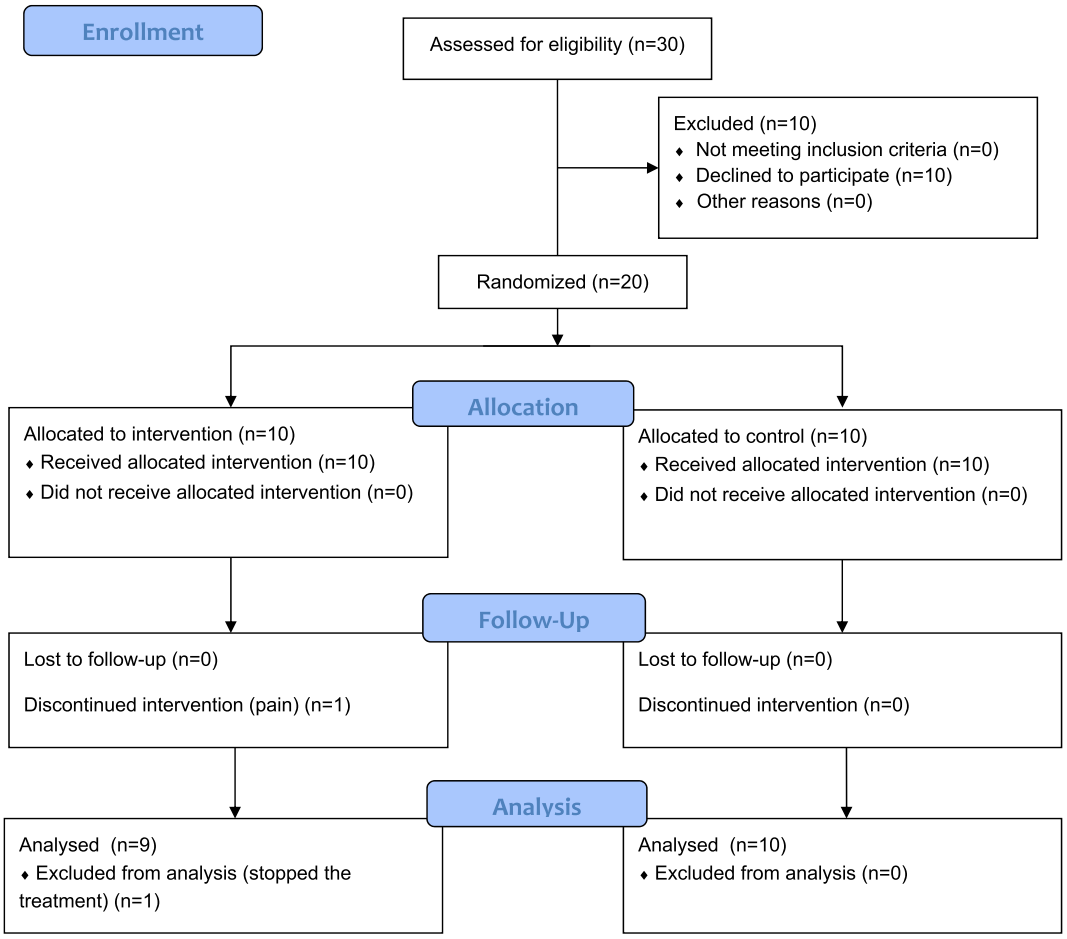

FIGURE 1 Consort flow diagram of the study [Color figure can be viewed at wileyonlinelibrary.com]

2.5 | Functional exercise capacity

The six-minute walk test (6MWT) was performed following the ERS/ATS guidelines (Holland et al., 2014) except for a noncontinuous recording of the pulsed oxygen saturation (SpO_2) (before and after the test). The same investigator supervised all tests. A training test was performed by the patient to avoid the learning effect.

Walking distance was expressed in absolute and predicted values (Enright & Sherrill, 1998). Dyspnea was measured by a visual analog scale. Pulsed oxygen saturation (SpO_2) and heart rate (HR) were measured by a pulse oximeter (Onyx, NONIN, MN). Variability during the test and the rest period was calculated by the difference between initial and final values (divided by the initial value for HR).

2.6 | Anxiety and depression

Patients completed the Hospital Anxiety and Depression Scale (HADS), which includes 7 items for anxiety (HADS-A) and 7 items for depression (HADS-D). The responses and both subscales were scored from 0 to 3 ("3" indicates higher symptom frequencies) and from 0 to 21 (21 indicates the most severe score). Scores are categorized as normal (0–7), mild (8–10), moderate (11–14),, and severe (15–21).

2.7 | Physical activity

The Baecke's questionnaire (Baecke, Burema, & Frijters, 1982) was used to assess patients' habitual physical activity. It includes 16 questions that relate to activities carried out at work, for sport, and for leisure. The questionnaire gathers information about the type of activity, the frequency of performance, and the number of months per year during which the subject performs the activity. Each domain results in a separate score that incorporates activity duration, frequency, and an intensity code based on energy costs. An index for the three domains was calculated. The higher the score, the more active the subject is.

TABLE 1 Age, anthropometric characteristics, lung function parameters, and inspiratory muscle strength in patients with hEDS who were evaluated in a routine outpatient visit

Number	104
Age (years)	40.7 ± 14.1 [37.9; 43.4]
Weight (kg)	72.2 ± 15.4
	[69.1; 75.2]
Height (cm)	166.0 ± 9.5
	[164.1; 167.8]
BMI (kg/m^2)	25.8 ± 5.1
	[24.8; 26.8]
FEV1/FVC (%)	79.3 ± 8.5
	[77.7; 81.0]
FVC (% predicted)	109.2 ± 16.5
	[106.0; 112.4]
FEV1 (% predicted)	101.7 ± 16.4
	[98.6; 104.9]
TLC (% predicted)	109.0 ± 12.2
	[106.3; 111.6]
SNIP (cm H_2O)	51.2 ± 21.2
	[47.0; 57.3]
SNIP (% predicted)	65.2 ± 30.2
	[59.3; 71.1]

Data are presented as the mean ± SD [95% confidence interval]
BMI: body mass index; FEV1: forced expiratory volume in one second; FVC: forced expiratory vital capacity; TLC: total lung capacity; SNIP: sniff inspiratory pressure.

2.8 | Statistical analysis

We calculated that 10 subjects per group were necessary to detect a difference of 15 cm H_2O on SNIP after IMT (average improvement determined from results of previous studies on patients with similar PImax (Beaumont, Forget, Couturaud, & Reychler, 2018)) while accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test. We assumed that 15 cm H_2O is the standard deviation (SD) of the difference in the response to treatment for the same patient. The SPSS 24.0 program (IBM software) was used to analyze the data.

TABLE 2 Age, anthropometric characteristics, hypermobility scores (Beighton: >5 [positive]), habitual physical activity scores and subscores during work, sport and leisure (Baecke: The higher the score, the more active the subject is), Hospital Anxiety and Depression Scale (HADS) scores pulmonary parameters and functional exercise performance at baseline in patients with hEDS allocated to either inspiratory muscle training (IMT group) or no intervention (control group)

	IMT group	Control group	Intergroup *p* values
Number	10	10	
Age (years)	45.8 ± 5.5	53.1 ± 3.4	.011*
	[34.9; 56.8]	[50.7; 55.5]	
Weight (kg)	72.4 ± 13.8	82.3 ± 13.2	.188
	[61.8; 83.0]	[72.9; 91.8]	
Height (cm)	163.7 ± 6.7	158.9 ± 20.9	.452
	[158.5; 168.8]	[144.0; 173.8]	
BMI (kg/m^2)	26.9 ± 3.8	29.6 ± 5.1	.401
	[24.0; 29.8]	[25.4; 33.9]	
Beighton score	5.9 ± 0.7	5.7 ± 0.5	.482
	[5.5; 6.3]	[5.4; 6.0]	
Baecke overall score	6.4 ± 2.4	6.8 ± 2.5	.591
	[4.9; 7.9]	[5.3; 8.3]	
HADS-A	11 ± 3	10 ± 5	.403
	[9; 13]	[6; 13]	
HADS-D	7 ± 3	7 ± 4	.901
	[5; 9]	[4; 9]	
SNIP	41 ± 17	41 ± 19	.990
(cm H_2O)	[28;53]	[27;55]	
FVC	115 ± 20	110 ± 13	.537
(% predicted)	[100;129]	[100;119]	
FEV1	94 ± 14	92 ± 21	.738
(% predicted)	[84;104]	[77;106]	
6MWD	455 ± 107	444 ± 128	.831
(meter)	[379;532]	[346;542]	

BMI: body mass index.
Data are presented as the mean ± SD [95% confidence interval].
HADS-A and HASD-D scoring: 0–7 (normal), 8–10 (mild), 11–14 (moderate), and 15–21 (severe).
*Statistically significant ($p < .05$).

Data were expressed as the mean ± SD (interquartile range) for normal variables or median (min-max) for those with non-normal distribution. Normality of the distribution was verified by the Kolmogorov–Smirnov test. The improvement of the different outcomes related to the training was calculated. Correlations between SNIP and lung function parameters and changes were verified by Pearson correlation coefficients. Comparison tests were either unpaired Student's t-tests or Wilcoxon tests, and the value of p <.05 was considered significant. The analysis used an intention-to-treat approach.

3 | RESULTS

3.1 | Prospective evaluation of lung function and IM strength in EHS-HT patients

One hundred and fifteen patients were eligible for an assessment of lung function and IM strength. Eleven subjects were excluded because of their smoking habit (n = 9) or sex (n = 2 males).

The anthropometric features and lung function test results of 104 subjects are shown in Table 1. Although FVC, forced expiratory volume in one second (FEV1), and TLC were in the normal range, 24% had a higher FVC than normal and 12% of subjects had a higher TLC than normal. No subject demonstrated a restrictive lung disease. SNIP values were lower than the lower limit of normal for 77% of the subjects. SNIP values were positively but weakly correlated to all lung function parameters (FVC: r = .311; p = .003; FEV1: r = .257; p = .019; TLC: r = .338; p = .002).

All these results suggest reduced IM strength despite preserved lung function.

3.2 | Randomized controlled trial about IMT in EHS-HT patients

Eighty of the 104 patients assessed for lung function and IM strength were eligible for the randomized controlled 6-week trial of IMT. Thirty patients with reduced IM strength had to be assessed for the randomized controlled trial to achieve the required sample size. Ten withdrew consent for the trial as the study visits did not fit their professional or

TABLE 3 Cardiopulmonary parameters, functional exercise performance, and emotional distress at both study entry (Week-0) and study end (Week-7) in patients with hEDS who either were subjected to daily inspiratory muscle training (IMT group) or received no intervention (control group)

	Week-0		Week-7		Week-7 versus Week-0	
	IMT group	Control group	IMT group	Control group	IMT group	Control group
FVC (% predicted)	115 ± 20 [100;129]	110 ± 13 [100;119]	116 ± 17 [102;131]	103 ± 18 [90;116]	p = .716	p = .047*
FEV1 (% predicted)	94 ± 14 [84;104]	92 ± 21 [77;106]	103 ± 11 [94;112]	89 ± 23 [73;105]	p = .010*	p = .241
SNIP (cm H_2O)	41 ± 17 [28;53]	41 ± 19 [27;55]	49 ± 18 [34;65]	38 ± 20 [24;52]	p = .003*	p = .088
6MWD (meter)	455 ± 107 [379;532]	444 ± 128 [346;542]	515 ± 127 [408;621]	465 ± 131 [371;559]	p = .036*	p = .195
Initial SpO_2 (%)	97.7 ± 1.7 [97.5;99.0]	97.2 ± 1.1 [96.4;98.1]	98.3 ± 0.5 [97.9;98.6]	97.5 ± 0.9[a] [96.8;98.2]	p = .968	p = .622
Final SpO_2 (%)	97.8 ± 2.6 [96.0;99.6]	96.7 ± 1.7 [95.4;97.9]	98.5 ± 0.5 [98.1;99.1]	97.2 ± 1.1[a] [96.4;98.0]	p = .516	p = .347
Change in dyspnea score	2.5 ± 2.0 [1.0;3.9]	2.9 ± 1.4 [1.8;3.9]	2.7 ± 1.4 [1.6;3.9]	2.2 ± 1.8 [0.9;3.5]	p = .580	p = .088
Initial heart rate (bpm)	93 ± 17 [81;105]	80 ± 11 [72;89]	82 ± 12 [72;93]	78 ± 10 [72;93]	p = .123	p = .346
Final heart rate (bpm)	108 ± 17 [96;118]	92 ± 10[a] [84;99]	106 ± 8 [100;112]	92 ± 10[a] [100;113]	p = .786	p = .784
Delta heart rate	17 ± 16 [5;29]	15 ± 10 [7;23]	31 ± 16 [18;44]	19 ± 10 [12;26]	p = .029*	p = .325
HADS-A	11 ± 3 [9;13]	10 ± 5 [6;13]	7 ± 4 [4;10]	10 ± 4 [7;13]	p = .115	p = .583
HADS-D	7 ± 3 [5;9]	7 ± 4 [4;9]	6 ± 4 [3;10]	9 ± 5 [6;13]	p = .951	p = .116

FVC: forced expiratory vital capacity; FEV1: forced expiratory volume in one second; SNIP: sniff inspiratory pressure; 6MWD: six-minute walking distance; SpO_2: pulsed oxygen saturation; bpm: beats per minute at the beginning (initial) and end (final) of the 6MWD test; Hospital Anxiety (HADS-A) and Depression (HADS-D) Scale.
Data are expressed as the mean ± SD [95% confidence interval].
[a]Significant difference between IMT and control groups (p < .05).
*p < .05 (statistically significant).

TABLE 4 Change of cardiopulmonary parameters, functional exercise performance and emotional distress in patients with hEDS who either were subjected to daily inspiratory muscle training (IMT group) or received no intervention (control group)

	IMT group	Control group	Intergroup *p* values
SNIP	13 ± 8	−3 ± 5	<.001*
(cm H_2O)	[6;20]	[−6;1]	
FVC	115 ± 20	110 ± 13	.237
(% predicted)	[100;129]	[100;119]	
FEV1	8.5 ± 6.9	−2.8 ± 7.7	.009*
(% predicted)	[2.7;14.3]	[−8.3;2.7]	
6MWD	64 ± 69	8 ± 17	.003*
(meter)	[5;121]	[−5;19]	
Change in dyspnea score	−0.4 ± 1.2	0.8 ± 1.8	.200
	[−1.9;1.2]	[−0.2;1.7]	
HADS-A	−2 ± 6	3 ± 4	.083
	[−7; 2]	[0; 5]	
HADS-D	0 ± 6	3 ± 5	.408
	[−5; 5]	[−1; 6]	

FVC: forced expiratory vital capacity; FEV1: forced expiratory volume in one second; SNIP: sniff inspiratory pressure; 6MWD: six-minute walking distance; SpO_2: pulsed oxygen saturation; bpm: beats per minute at the beginning (initial) and end (final) of the 6MWD test; Hospital Anxiety (HADS-A) and Depression (HADS-D) Scale.
Data are expressed as the mean ± SD [95% confidence interval].
*p < .05 (statistically significant).

family schedule. Therefore, 20 patients were randomly allocated to a control or treatment group and assessed between July and October 2015 (Figure 1). One patient stopped the training after 3 weeks because of thoracic pain. Adherence was 98.4%, with seven out of the nine remaining patients completing the program and performing all the prescribed sessions.

Table 2 gives age, anthropometric characteristics, hypermobility scores (Beighton), habitual physical activity scores and subscores during work, sport, and leisure (Baecke), and Hospital Anxiety and Depression Scale (HADS) scores at baseline in patients with hEDS allocated to the control and IMT groups. At baseline, there was no statistically significant difference between the two groups. Only age differed significantly between the groups (p = .011).

Table 3 gives relevant parameters for the cardiopulmonary function, functional exercise performance, and emotional distress recorded at the start and at the end of the trial. At baseline, there was no statistically significant difference between the two groups. Patients had dramatically weakened IMs (SNIP averaging 49% of the predicted values). FVC exceeded the upper limit of the normal range in 30% of patients and FEV1 was in the normal range for all patients. Functional exercise performance was normal (six-minute walking distance [6MWD] averaging 107% of the reference distances), and the 6MWT-induced heart rate or dyspnea evolutions were similar in both groups. The HADS-A (anxiety part) score was mild–moderate and the HADS-D (depression part) score was normal.

At study completion (Table 3; Week-7), some significant changes were observed from baseline values. FVC was slightly (−6%), albeit significantly (p = .047), decreased in the control group. In the IMT group, FEV1 improved by 9%, the SNIP value increased from 41 to 49 cm H_2O, walking distance improved by 13%, and the 6MWT-induced heart rate variation doubled.

Improvement was significantly different between both groups only for SNIP, FEV1, and 6MWT (Table 4). All treated patients had a SNIP and 6MWD improvement that was greater than the corresponding minimal clinically important difference (MCID) (based on data from patients with stable heart rate failure or COPD by lack of specific data). Indeed, SNIP gain reached 20% for an MCID of 14%, and 6MWD improved by 60 m for an MCID of 35 m (Puhan et al., 2008; Tager et al., 2015). However, the IM strength remains lower than the predicted values in the IMT group (58% of predicted). Moreover, the SNIP and 6MWD improvements were correlated (r = .535; p = .022). The IMT also almost tripled the FEV1 target value (285 mL for an MCID of 100 mL [Donohue, 2005]). The SNIP improvement was neither correlated with the FEV1 improvement (r = −0.022; p = .959) nor with the FVC improvement (r = −0.138;– p = .744).

There were no significant changes in SpO2, dyspnea score, or anxiety and depression scores between study inclusion and completion. The anxiety and depression scores were normal or mild in the two groups at study completion. The improvement of anxiety tended to be different between both groups.

This part of the study highlights the benefit of IMT on muscle function and functional exercise performance even if the IM strength is not completely restored.

4 | DISCUSSION

To the best of our knowledge, this is the first study to explore IM strength in hEDS, which is often associated with dyspnea, fatigability, and limited walking distance (Castori, Camerota, Celletti, Danese, et al., 2010), and for which no cures exist. Two important findings emerged from this study. First, we found that patients have a marked IM weakness as evidenced by a dramatic reduction in the SNIP values and a tendency toward greater lung volumes as illustrated by higher FVC and TLC than normal. Second, we showed that a 6-week outpatient IMT protocol with a pressure threshold device positively impacts SNIP, FEV1, and functional exercise performance as measured by the 6MWT. Although IM strength was not restored to normal levels after the trial, the significant increase in SNIP indicates a remarkable improvement.

SNIP is a reliable test that measures the strength of the diaphragm (Fitting, 2006) and that easily monitors patients at risk of developing respiratory insufficiency (Soliman et al., 2005), conveys a strong predictive power for mortality in chronic obstructive pulmonary disease (Moore et al., 2010), and is even better than PImax and vital capacity in predicting hypercapnia (Fitting, 2006).

As the strength of the IMs positively affects PImax and chest wall mobility (Lanza et al., 2013), the reduction in SNIP values in nearly 80% of the patients indicates marked IM weakness and explains, at least in part, the breathing difficulties experienced by these patients. The mean absolute value was lower than in the most severe COPD patients (Donaria et al., 2014). Glucocorticotherapy, malnutrition, and chronic hypoxia often contribute to the reduced force of respiratory

and limb muscles that are observed in patients with chronic pulmonary diseases (Decramer, Lacquet, Fagard, & Rogiers, 1994). However, steroids, hypoxia, and malnutrition are usually absent in EDS and were not present in our patients.

In patients with EDS, a sedentary lifestyle may cause muscle weakness as patients from our randomized trial had a reduced physical activity score (Hertogh, Monninkhof, Schouten, Peeters, & Schuit, 2008). The causes of relative inactivity might be related to pain, fatigue, and hypermobility and instability of joints. IMT improved respiratory and peripheral muscle strength and decreased dyspnea perception in patients with other diseases (heart failure, COPD) (Bosnak-Guclu et al., 2011; Petrovic, Reiter, Zipko, Pohl, & Wanke, 2012) even if inconsistent results have been found, probably depending on the combination with pulmonary rehabilitation (Beaumont et al., 2018). We found that our IMT protocol led to clinically relevant and statistically significant improvements in FEV1, functional exercise performance, and IM strength. The effect of IMT on SNIP impacts both FEV1 and absolute heart rate and would explain the observed improvement in the 6MWT (Casanova et al., 2011). The generated dyspnea during the 6MWT (change in dyspnea score) was not improved in IMT group. However, even if there was no difference in change of dyspnea generated by the 6MWT between both groups, the evaluation was not performed at the same level of exertion in the IMT group compared to the control group. Indeed, patients from the IMT group walked a longer distance with a similar level of dyspnea at the end of the training. It suggests that the dyspnea could be improved at the same level of exertion due to the IMT.

Even if the benefit of IMT on anxiety was not significant, it was clinically relevant based on the MCID based on data from COPD patients (Smid et al., 2017). As IMT nearly tripled the MCID of HADS-A (4 vs. 1.5), it could suggest that the patients felt an improvement in anxiety in the training group.

Further studies will be required to determine the optimal settings of the program. We could hypothesize that a longer training duration and supervised sessions could demonstrate a greater improvement in IM strength. Longer duration of training has been previously suggested in COPD (Hill, Cecins, Eastwood, & Jenkins, 2010). The IM strength of our patients was possibly too reduced to be restored in 6 weeks. Moreover, our sessions were unsupervised and lower improvements with unsupervised compared to supervised programs were previously noted in other studies (Lacroix, Hortobagyi, Beurskens, & Granacher, 2017).

The extracellular matrix (ECM) of connective tissue provides significant structural and biochemical support to skeletal muscles and peripheral nerves. In rare cases of hEDS, the reduction in body levels of tenascin-X causes neuromuscular dysfunction (Voermans, Altenburg, Hamel, de, & van Engelen, 2007), whereas in a case of more common/prevalent EDS, muscle weakness results from alterations in the connective tissue surrounding muscle cells (Bilkey, Baxter, Kottke, & Mundale, 1981). In our study, all patients had significant ultrastructural changes in their dermal collagen network, and 60% had abnormal elastic fibers. Although we did not carry out biopsies of patients' respiratory muscles, it is reasonable to assume that similar defects in the neuromuscular ECM reduce muscular contraction and interfere with the myotendinous transmission of the force (Voermans et al., 2007). There is evidence that forces generated within muscle fibers are transmitted onto the intra-, inter-, and extra-muscular connective tissue to the skeleton, that is, via a myofascial transmission (Huijing et al., 2010). Thus, a decrease in myofascial transmission could result in the muscle weakness as observed in patients with EDS (Voermans et al., 2007).

Musculoskeletal pain and fatigue are frequently reported by patients with hEDS and likely contribute to muscle weakness. As these outcomes were not quantified in the study, their relationship with our results is not possible to be discussed. Fatigue intensity modulates muscle function (Henriksen et al., 2007), correlates with a reduction in muscle strength (Voermans, Knoop, Bleijenberg, & van Engelen, 2011), and presumably worsens with exercise (Rombaut et al., 2012). As experimental muscle pain by infusions of hypertonic saline inhibits maximal voluntary contractions through a central mechanism(Graven-Nielsen, Lund, Arendt-Nielsen, Danneskiold-Samsoe, & Bliddal, 2002), the chronic and severe musculoskeletal pain seen in patients with hEDS (Voermans et al., 2010) possibly causes submaximal contraction and maintains muscle weakness.

Lung function was normal, but a large proportion of patients tended to have greater lung volumes. The increased lung volume can also be explained by the defects in neuromuscular ECM and the hypermobility of thoracic joints in these patients.

The relatively small number of patients is a limitation of this randomized controlled study, even if the number of included patients corresponds to the minimum sample size required to achieve adequate statistical analysis. We also studied a homogeneous population regarding age, sex, anthropometric parameters, past and ongoing lung diseases, clinical diagnosis and ultrastructural abnormalities of dermal collagen fibers. Another study limitation is the lack of magnetic or phrenic nerve stimulation to ensure maximal diaphragm contractility during SNIP measurements (Fitting, 2006). However, these approaches are expensive, may overestimate diaphragmatic strength, and might be inappropriate in patients with hEDS who barely tolerate invasive explorations and who bleed easily. Moreover, neither quality of life nor dyspnea at a similar exertion level was evaluated in our study. Notwithstanding such limitations, at study completion, SNIP values did not change from baseline in the untreated control group but increased markedly in the group performing daily inspiratory training. The use of MCID from patients with COPD is also a limitation for the interpretation. Indeed, it is important to mention that applying MCID established in another chronic respiratory disease to hEDS could be imprecise. All forms of patient variation such as symptoms influence the MCID of an outcome (Copay, Subach, Glassman, Polly Jr., & Schuler, 2007; Lauridsen, Hartvigsen, Manniche, Korsholm, & Grunnet-Nilsson, 2006). Such variations can be expected between COPD and hEDS. However, MCID have never been determined in patients with hEDS for theses outcomes.

In conclusion, patients with hEDS have a significant IM weakness that can account for dyspnea and contribute to the impairment of mobility and daily activities. The IMT protocol used in this randomized controlled trial achieved clinically significant increases in both respiratory and exercise capacity, although the improved SNIP values remained below 80% of the reference values. Anxiety and depression scores did not change significantly between the treated and control

groups. IMT should be considered in usual care of the patient with hEDS to improve breathing difficulties and exercise capacity.

ACKNOWLEDGMENT

Gregory Reychler received a grant from the Institut de Recherche Expérimentale et Clinique (Université catholique de Louvain – Brussels – Belgium).

CONFLICT OF INTEREST

The authors declared that they have no conflict of interest. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare; no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

AUTHORS' CONTRIBUTIONS

RG: Substantial contributions to the conception, design of the work and the acquisition, analysis and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; LG: Substantial contributions to the conception of the work and the interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; GEP: substantial contributions to the acquisition, analysis and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; TH-Lê: Substantial contributions to the acquisition and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published; MD: substantial contributions to the conception, design of the work and the acquisition, analysis and interpretation of data for the work; drafting the work and revising it critically for important intellectual content; final approval of the version to be published. All authors had full access to statistical reports and tables in the study. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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How to cite this article: Reychler G, Liistro G, Piérard GE, Hermanns-Lê T, Manicourt D. Inspiratory muscle strength training improves lung function in patients with the hypermobile Ehlers–Danlos syndrome: A randomized controlled trial. *Am J Med Genet Part A*. 2018;1–9. https://doi.org/10.1002/ajmg.a.61016