A RANDOMISED CONTROLLED TRIAL OF ADJUNCTIVE INSPIRATORY MUSCLE TRAINING FOR PATIENTS WITH COPD – ONLINE DATA SUPPLEMENT

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MATERIAL AND METHODS

For the full study protocol see http://bmjopen.bmj.com/content/bmjopen/3/8/e003101.full.pdf

Study Design and Patients

This multicentre, double-blind, randomised controlled study was performed simultaneously at 5 different rehabilitation centres (University Hospital Leuven, Belgium; University Hospital Ghent, Belgium; Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Quebec, Canada; University Hospital Nijmegen, The Netherlands; and Schön Klinik Berchtesgadener Land, Germany). All patients with spirometry-proven COPD who were referred for pulmonary rehabilitation during the study period were screened for inclusion. The study was approved centrally by the University Hospital Leuven's Institutional Review Board (Approval Number ML7489) as well as from all other relevant local centre committees and was registered in an international trial registry database (clinicaltrials.gov: NCT01397396). Clinically stable COPD patients with reduced maximal inspiratory mouth pressure (PImax <60 cmH_2O or <50% of the predicted normal value)[1] were eligible for participation. Exclusion criteria were (1) diagnosed psychiatric or cognitive disorders; (2) progressive neurological or neuromuscular disorders; (3) severe orthopedic problems having a major impact on daily activities; and (4) previous inclusion in a rehabilitation programme (<1 year).

Randomisation and masking

Patients were informed about the study protocol prior to the start of the rehabilitation programme and informed consent was obtained at that time. Patients were subsequently randomised to either an intervention or a control group. Concealment of group allocation was achieved by simple randomisation using sealed opaque envelopes in random block sizes of 4 and 6 (order unknown to investigators) according to a published protocol.[2] Details on sample size estimation and power calculation for the primary outcome are described in more detail in the online data supplement and in the published study protocol.

Sample size calculation

To detect a minimally clinically important difference between groups of 26m in the 6-minute walking distance (6MWD),[3] assuming a standard deviation of the within group differences in the 6MWD at the end of the intervention period of 60 m in both groups with a degree of certainty (statistical power) of 80% and a risk for a type I error (α) < 5%, minimally 85 patients were calculated to be included in each group, given an anticipated dropout rate of 30%. This study therefore was performed as a multicentre randomised, double-blind, controlled trial to ensure inclusion of 170 patients within a time-frame of two years. Besides the lead centre at the University Hospital in Leuven, Belgium, patients were also recruited in the Ghent University Hospital, Belgium; Université Laval Quebec, Canada; Radboud University Nijmegen Medical Centre, The Netherlands; and Schoen Klinik Berchtesgadener Land, Germany. Each of the five centres was expected to include between 30 to 40 patients within the two year inclusion period.

Interventions

Intermediate measurements of PImax were performed once weekly in both groups (intervention and control). The IMT programme was described to participants either as ‘respiratory muscle strength training’ (intervention group) or ‘respiratory muscle endurance training’ (control group). Training intensity in the control group was set at 10% baseline PImax and was not modified throughout the intervention period. Training intensity in the intervention group was adapted during supervised

sessions. The training loads were adjusted according to a previously published protocol.[4] We aimed to initiate IMT in the intervention group at a minimum of 40% of baseline PImax. . The a priori aim in the intervention group was to increase training loads during the programme to equal at least 50% of the patients' actual PImax in every week. Rates of perceived inspiratory effort on a modified CR-10 Borg Scale,[5] subjective impressions of physiotherapists during supervised sessions, and flow-volume response during the training sessions were taken into account to determine the highest tolerable load for each individual patient. Compliance with the IMT was assessed by analyzing objectively registered, and automatically stored training session parameters (pressure, flow, power, and work) in both groups. Physiotherapists compared performance data during supervised sessions with results from home-based sessions to elicit full effort during unsupervised IMT sessions.

Outcome measurements

More details about outcome measurements are provided in a video tutorial (see supplementary video files 1, 2, 3, and 4) and in the published study protocol.[4]

6-minute walking distance (6MWD). Functional exercise capacity was measured using a six-minute walking test in a 50 m corridor. Standardized encouragement was provided.[6] The best of two tests separated by recovery time 30 minutes was used and related to reference values.[7] Oxygen saturation, heart rate and symptoms of leg effort and dyspneoa were recorded before and after the test.

Inspiratory muscle strength. PImax was recorded at the mouth as a surrogate of inspiratory muscle force. Measurements were performed from residual volume using the technique proposed by Black and Hyatt.[8] An electronic pressure transducer was used (MicroRPM; Micromedical, Kent, UK). Assessments were performed on two separate days and were repeated at least 5 times on each occasion until the three best measurements differed from each other by less than 5cmH_2O. Reference values published by Rochester and Arora were used to define normal respiratory muscle force.[9]

Inspiratory muscle endurance. Patients were asked to breathe against a sub maximal inspiratory load provided by the TFRL device (POWERbreathe® KH1, HaB International Ltd., Southam, UK) until task failure due to symptom limitation (Tlim). At baseline an inspiratory load was selected that allowed patients to continue breathing for 3-7 minutes. After an initial familiarization trial at 40% PImax the load was either increased or decreased for the next test based on the performance of the patient during the trial. Up to two additional trials were performed on the same day to determine a load that would allow patients to continue breathing for 3-7 minutes. On a separate day the test was repeated at least once against the established load and the best result was recorded as the baseline Tlim. Breathing instructions were the same as during the training sessions. Number of breaths, average inspiratory time (Ti) as a fraction of the total respiratory cycle duration (Ttot), average mean load, average mean power, and total external inspiratory work were derived from continuous measurements of flow and pressure during the test and recorded by the previously validated electronic loading device.[10] The endurance test was repeated using an identical load at post-training. Improvements in Tlim and changes in breathing parameters were recorded as main outcomes. A limit of 15 minutes was handled as the maximum duration of the test performed after 8 weeks. In case patients were not symptom limited at this time point the assessor stopped the test.

Maximal exercise capacity (incremental exercise test). Maximal exercise capacity was assessed by a maximal incremental cycle exercise test (Ergometrics 900, Ergoline, Bitz, Germany). After a 2 min resting period and 3 min of unloaded cycling, patients started cycling at a load of 20W. Load was then increased by 10W/min and patients cycled until symptom limitation. Oxygen uptake, carbon dioxide output and ventilation were measured breath by breath (Vmax series, SensorMedics, Anaheim, California, USA). Heart rate and oxygen saturation were recorded continuously. Maximal oxygen uptake was compared with normal values.[11] The perception of dyspnoea and leg effort was be quantified at 1 min intervals during exercise and at the end of the test using the modified Borg scale. [5] The development of dynamic hyperinflation during the exercise test was assessed by

recording the changes in end-expiratory lung volumes during repeated measurements of inspiratory capacity every two minutes during exercise.[12]

Endurance exercise capacity (constant work rate test). A constant power output cycle test until symptom limitation was performed at 80% of the maximal power output (in Watts) that was reached during an initial incremental exercise test (Ergometrics 900, Ergoline, Bitz, Germany). Oxygen uptake, carbon dioxide output and minute ventilation were measured breath-by-breath (Vmax series, SensorMedics, Anaheim, CA). Breathing pattern and dynamic hyperinflation were monitored as described previously for the incremental cardiopulmonary exercise test. Heart rate and oxygen saturation were monitored continuously. The perception of dyspneoa and leg effort were quantified at two-minute intervals during exercise and at the end of the test using the modified CR-10 Borg scale.[5]

Statistical analyses

A p-value of <0.05 was taken as a threshold for statistical significance. Graphical presentations were produced with Prism 5 (GraphPad Software, San Diego, CA, USA). Data are presented either as mean ± standard deviation or as mean ± standard error of the mean. Within group changes were analysed using paired t-tests. Progression of training parameters between groups were compared with two-way ANOVA analyses with Bonferroni corrections of post-hoc tests at different time points. To account for potential differences between GET programmes offered in the different centres we tested the effect of 'centre' on treatment effects using centre*intervention effect. The effects in the centre offering a 20 GET sessions were compared with the other centres offering 36 sessions. For post hoc comparisons two groups were created from the 4 centres offering higher training volume. The centre with the largest contribution to overall recruitment (32% of total inclusions) was analysed separately while the other three centres (32% combined of total inclusions) were grouped together. These two groups were compared to the centre offering 20 GET sessions (36% of total inclusions).

Additional exploratory analyses were performed by pooling data of intervention and control group, subsequently dividing it into tertiles based on improvements in PImax, and testing differences using

general linear models. Stepwise multiple regression was used to investigate which IMT characteristics were most closely associated with improvements in PImax. The relationship between improvements in PImax and the following independent variables were explored: Age, gender, BMI, baseline FEV_1 (%pred), baseline FRC (%pred), as well as training parameters of IMT sessions (average peak power, training intensity, total work performed and number of training sessions completed).

In additional adjusted analyses differences in 6MWD and endurance cycling time between the intervention and the control group after the intervention were compared, adjusting for two confounding baseline variables (FVC% pred and Quadriceps strength %pred) in addition to baseline values of the outcome variable itself. These additional variables were retained since they were not equally distributed between groups at baseline and influenced the estimate of the effect. Other potential confounders (degree of hyperinflation) were not retained in the final adjusted model.

Results

The contributions of each centre in terms of recruitments during the four years inclusion period were as follows: University Hospital Leuven 32%, Ghent University Hospital 21%, Université Laval 7%, University Hospital Nijmegen 4%, and Schoen Klinik Berchtesgadener Land 36% of total inclusions. Adjusting between group differences in 6MWD and endurance cycling time (in addition to baseline values of respective outcomes) for two other confounding baseline variables did not have a major impact on the results of these analyses (see Table E6 below).

GET progression

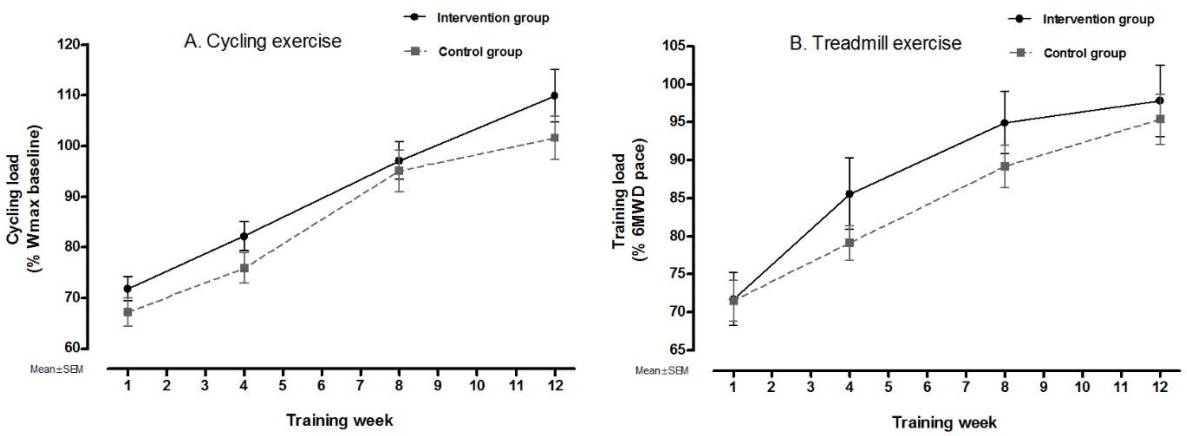

Figure E1: Progression of the general exercise training in the intervention and control group; A) cycling training load in percentage of the peak work rate at baseline; B) treadmill training load in percentage of the 6MWD pace at baseline, values represented as mean±SEM.

IMT progression

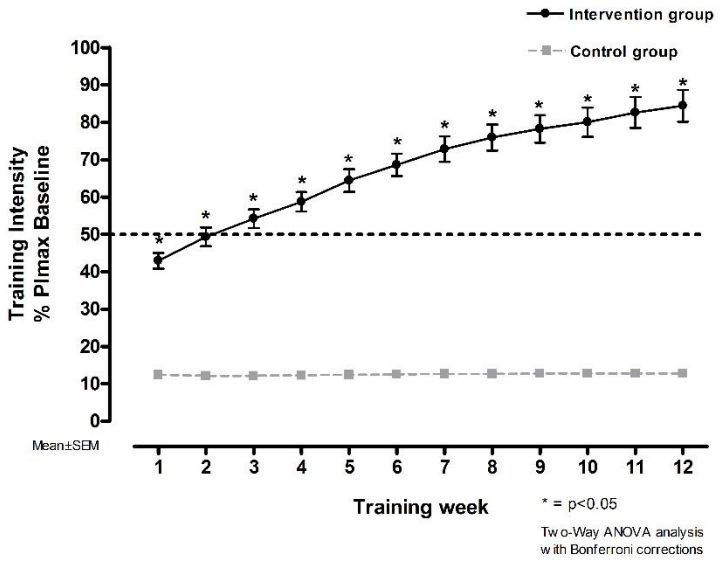

Figure E2: Progression of training intensity expressed as a percentage of baseline PImax. * = $p<0.05$ between groups. Dotted line represents target training intensity in the intervention group.

Table E1 Baseline characteristics of completers and patients who were lost to follow-up.

Variables	Completers (n=174)	Lost to follow-up (n=45)	p-value
Age (yr)	66±7	65±7	0.862
BMI (kg/m^2)	25±6	24±6	0.409
FEV_1 (%predicted)	42±16	38±14	0.145
FVC (%predicted)	72±21	72±21	0.881
FEV_1/FVC (%)	46±14	43±14	0.263
TLC (%predicted)	123±25	125±22	0.794
FRC (%predicted)	181±45	179±54	0.819
RV (%predicted)	211±70	210±63	0.935
DLCO (%predicted)	43±21	36±19	0.099
PImax (%predicted)	52±15	47±14	0.035*
Endurance breathing time (sec)	248±107	220±78	0.076
Peak VO_2 (%predicted)	68±28	55±26	0.018*
Peak work rate (%predicted)	49±22	34±24	0.002*
Endurance cycle time (sec)	279±145	253±143	0.394
6MWD (%predicted)	58±18	48±20	0.001*
Quadriceps strength (%predicted)	76±31	71±27	0.378
Hand grip strength (%predicted)	90±25	80±22	0.028*
CRQ dyspnoea	15±6	14±5	0.303
mMRC	2.5±1.1	3.0±1.2	0.039*

Data are presented as mean ± SD. Abbreviations: FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; TLC= total lung capacity; FRC = functional residual capacity; RV = residual volume; PImax = maximal inspiratory mouth pressure; 6MWD = six minute walking distance; Peak VO_2 = peak oxygen uptake; Peak work rate = peak power output during a maximal incremental cycle ergometry test; CRQ = chronic respiratory questionnaire; mMRC = modified Medical Research Council dyspnoea; %pred = percentage of the predicted value.* indicates a statistically significant between group difference ($p<0.05$).

Table E2 Changes in pulmonary function

Variables	Intervention group		Control group		Adjusted difference (95%) at post training	p-value*
	Pre-training	Post-training	Pre-training	Post-training		
FEV_1 (L)	1.0 (0.4)	1.1 (0.4)	1.1 (0.5)	1.1 (0.5)	-0.01 (-0.06 to -0.05)	0.816
FVC (L)	2.2 (0.7)	2.5 (0.7)#	2.4 (0.8)	2.4 (0.9)	0.14 (0.02 to 0.26)	0.028
FEV_1/FVC (%)	46 (15)	45 (14)	45 (12)	45 (14)	-0.97 (-3.7 to 1.8)	0.483
MVV (L/min)	40 (17)	42 (17)#	41 (15)	42 (18)	1.2 (-1.4 to 3.8)	0.364
TLC (L)	7.1 (1.6)	7.1 (1.5)	7.2 (1.6)	7.2 (1.6)	-0.05 (-0.26 to 0.16)	0.644
FRC (L)	5.6 (1.4)	5.5 (1.3)	5.5 (1.5)	5.5 (1.4)	-0.03 (-0.25 to 0.20)	0.826
RV (L)	4.7 (1.4)	4.5 (1.3)	4.7 (1.6)	4.6 (1.5)	-0.08 (-0.33 to 0.16)	0.501
DLCO (mmol/min/Kpa)	6.8 (4.7)	7.1 (5.3)	6.3 (4.9)	6.3 (5.1)	0.26 (-0.34 to 0.86)	0.383

Data are presented as mean ± SD. Abbreviations: FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; PIF = peak inspiratory flow; TLC = total lung capacity; FRC = functional residual capacity; RV = residual volume; DLCO = diffusing capacity of the lungs for carbon monoxide. Analyses are based on 163 (FEV_1, 94% of completers) patients. #indicates a statistically significant difference within groups ($p<0.05$), *p-values are reported for between group comparisons (ANCOVA of post-training values adjusted for baseline values as covariates).

Table E3 Changes in chronic respiratory questionnaire (CRQ), participation in daily physical activity (PA), and limb muscle force

Variables	Intervention group		Control group		Adjusted difference (95%) at post training	p-value*
	Pre-training	Post-training	Pre-training	Post-training		
CRQ Dyspnoea	15 (6)	20 (6)#	15 (5)	19 (7)#	0.4 (-1.1 to 2.0)	0.601
CRQ Fatigue	16 (5)	19 (5)#	15 (4)	18 (5)#	0.4 (-0.8 to 1.6)	0.494
CRQ Emotion	30 (9)	35 (9)#	30 (9)	35 (8)#	-0.4 (-2.4 to 1.6)	0.698
CRQ Control	18 (5)	21 (5)#	17 (6)	19 (5)#	0.01 (-1.19 to 1.21)	0.985
CRQ Total	80 (21)	94 (23)#	76 (20)	92 (22)#	-1.0 (-5.19 to 3.9)	0.681
PA (steps/day)	3791 (2284)	3958 (2253)	4258 (1892)	4506 (1899)	-206 (-923 to 512)	0.568
Quadriceps Force (N)	156 (88)	173 (96)	162 (102)	180 (115)	-1 (-12 to 10)	0.913
Handgrip Force (kg)	29 (9)	31 (8)	29 (9)	30 (9)	1 (-1 to 2)	0.321

Data are presented as mean ± SD. Abbreviations: CRQ = chronic respiratory questionnaire; PA = participation in daily physical activity. Analyses are based on 150 (CRQ, 86% of completers) patients. #indicates a statistically significant difference within groups ($p<0.05$), *p-values are reported for between group comparisons (ANCOVA of post-training values adjusted for baseline values as covariates).

Table E4 Between group post treatment differences in centres offering 36 GET sessions in comparison with the centre offering 20 GET sessions (REF=reference centre).

	Post PImax (cmH_2O)	**Cycling intensity final week GET (% baseline PWR)**	**Post 6MWD (m)**	**Post endurance cycling time (sec)**
Centre offering 20 session programme (36% of total inclusions)	REF	REF	REF	REF
Centre offering 36 session programme (n=1; 32% of total inclusions)	+11 (4) (p=0.01)	+8 (11) (p=0.45)	+23 (16) (p=0.15)	+230 (92) (p=0.01)
Other centres offering 36 session programme (n=3; 32% of total inclusions)	-3 (4) (p=0.47)	-14 (11) (p=0.24)	-23 (16) (p=0.16)	-87 (85) (p=0.31)

Data are presented as mean (SE). Abbreviations: PImax = maximal inspiratory mouth pressure; GET = general exercise training; PWR = peak work rate; 6MWD = six minute walking distance; p-values are reported for post-hoc comparisons of post treatment differences among groups between centres offering higher training volumes and the centre offering a lower training volume (reference centre).

Table E5 Results of uni- and multivariate regression analyses of determinants of improvements in PImax

Variables	**Univariate**		**Multivariate (stepwise)**	
	β	p-value	β	p-value
Total work performed (J)	0.16	<0.001	0.18	<0.001
Baseline PImax (cmH_2O)	-0.15	0.071	-0.32	<0.001
Training volume (% of training sessions completed)	-0.10	0.079	-0.07	0.139
Age (yr)	-0.11	0.463	-	-
Sex (0= female; 1=male)	5.23	0.016	-	-
BMI (kg/m^2)	0.44	0.015	-	-
Baseline FEV_1 (%pred)	0.09	0.068	-	-
Baseline FRC (%pred)	-0.03	0.332	-	-
Avg peak power (W)	2.21	<0.001	-	-
Training intensity final IMT session (% baseline PImax)	0.20	<0.001	-	-

Abbreviations: J = joules; PImax = maximal inspiratory mouth pressure; FEV_1 = forced expiratory volume in one second; FRC = functional residual capacity.

Table E6 Adjusted analyses of between group differences in exercise-related outcomes

Variables	**Pre- training**	**Post-training**	**Pre-training**	**Post-training**	**Difference (95% CI) at Post-training***	**Adjusted Difference (95% CI) at Post-training^{+}**
Functional exercise capacity	**Intervention group**		**Control group**			
6MWD (m)	353 (116)	388 (113)$^{\#}$	374 (102)	407 (105)$^{\#}$	0.3 (-13 to 14) p=0.967	0.7 (-13 to 15) p=0.921
Endurance exercise capacity	**Intervention group**		**Control group**			
Endurance cycle time (sec)	271 (126)	496 (309)$^{\#}$	303 (163)	466 (292)$^{\#}$	75 (1 to 149) p=0.048	98 (17 to 179) p=0.018

Data are presented as mean (SD). Analyses are based on 169 (6MWD, 97% of completers) and 139 (endurance cycle time, 80% of completers) patients. $^{\#}$ indicates a statistically significant difference within groups ($p<0.05$), * results of between group comparisons (ANCOVA of post-training values adjusted for baseline values of outcomes as covariates), $^{+}$ results of between group comparisons (ANCOVA of post-training values adjusted for FVC% pred baseline, quadriceps strength % pred baseline, and baseline values of outcome as covariates).

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