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Short communication

Impact of mild-to-moderate exacerbations on outcomes of neuromuscular electrical stimulation (NMES) in patients with COPD

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ABSTRACT

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are common among patients attending pulmonary rehabilitation (PR) and may compromise its outcomes. Neuromuscular electrical stimulation (NMES) seems one of the few exercise modalities that can actually be continued during AECOPD, due to its low burden on the impaired respiratory and cardiovascular system. However, the quality of evidence is low. The purpose of this study was to assess the impact of mild-to-moderate AECOPD on adherence/outcomes of a high-frequency (HF) or low-frequency (LF) NMES training program, as part of inpatient PR, in severely dyspneic, weakened individuals with COPD. 62 patients who received NMES as the sole supervised muscle training modality during an 8-week PR program (HF-NMES: n = 33; LF-NMES: n = 29) were analyzed retrospectively. 48.4% experienced ≥1 AECOPD during PR and were classified as exacerbators. Exacerbators completed 75 NMES sessions (interquartile range: 73–78) and were able to increase training intensity with 24 mA (15–39), while non-exacerbators completed 76 sessions (73–79) and increased training intensity with 35 mA (22–50), with no between-group differences ($p = 0.474$ and $p = 0.065$, respectively). The median change in 6-min walking distance, cycle endurance time, and isokinetic quadriceps strength and endurance did not differ between the exacerbation and non-exacerbation group. To conclude, the occurrence of mild-to-moderate AECOPD during a PR program primarily focused on NMES, does not affect adherence, intensity, and clinical outcomes in patients with severe COPD. Continuing NMES seems a feasible way to potentially counteract exacerbation-related lower-limb muscle dysfunction and improve outcomes of PR, with HF-NMES being the preferential muscle training modality.

1. Introduction

The natural course of chronic obstructive pulmonary disease (COPD) is characterized by acute exacerbations (AECOPD), which are defined as acute worsenings of respiratory symptoms that result in additional therapy [1]. Even though pulmonary rehabilitation (PR) has the potential to improve outcomes after AECOPD [2], it cannot prevent the manifestation of exacerbations during the program [3]. AECOPD which result in hospitalization generally cause further physical inactivity [4] and quadriceps muscle weakness [5]. Therefore, it seems reasonable to hypothesize that the occurrence of AECOPD during a PR program may compromise its outcomes. While conventional exercise training is generally hindered in AECOPD [6], patients may be able to continue a muscle training strategy with a low burden on the impaired respiratory and cardiovascular system [7,8] like neuromuscular electrical stimulation (NMES) [9,10]. In fact, a 6 week home-based NMES training program has been safely and effectively applied in a small group of severely dyspneic patients with advanced COPD, even in the presence of AECOPD

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[11]. As AECOPD may unexpectedly occur during PR programs and NMES may potentially be one of the few exercise modalities that can actually be continued, we aimed to assess the impact of mild-to-moderate AECOPD on adherence and outcomes of a NMES training program in severely dyspneic individuals with COPD.

2. Material and methods

The current study is a retrospective analysis of the '*DICES trial*' (NTR2322). The ethics committee of the Maastricht University Medical Centre+ (MREC 11-3-070) approved this trial. All procedures were in accordance with the 'Declaration of Helsinki' [12] and all patients gave written informed consent. Design and efficacy data of the DICES trial have been published [8,13,14]. In brief, patients with COPD [1], with mMRC dyspnea grade 3–4, and quadriceps weakness [15] were randomly assigned to 80 inpatient supervised sessions (8 weeks, twice per day, five times per week) of high-frequency (HF; 75 Hz) or low-frequency (LF; 15 Hz) NMES of the quadriceps and calf muscles, bilaterally. Each session involved 18 min of symmetrical biphasic stimulation (Tensmed S84, Enraf-Nonius, Rotterdam, the Netherlands) with pulse duration of 400 μs, total cycle length of 8s on and 8s off and intensity adjusted to individual toleration. Participants were blinded for the NMES frequency and received no additional endurance or resistance training during their PR program.

Patients were evaluated at baseline and at the end of PR. Each evaluation included anthropometric measurements, whole body dual-energy x-ray absorptiometry (DXA-scan) [16], pulmonary function testing, measurements of quadriceps strength and endurance (i.e. isokinetic peak torque and total work) [17], as well as a 6-min walking test (6MWT) [18] and constant-work rate cycle test (CWRT) [19]. Procedures are detailed further in previous work [14].

Mild-to-moderate AECOPD were defined as 'acute increases in respiratory symptoms requiring additional rescue inhaler use and/or antibiotics and/or systemic glucocorticosteroid treatment' [3]. Patients were categorized into 'exacerbators' (≥1 AECOPD during PR) and 'non-exacerbators' (0 AECOPD during PR). Patients were transferred to the NMES training room during AECOPD or, in bed-bound patients, NMES was applied at the bed. Because the data were not normally distributed, results are presented as median and interquartile range (IQR). Mann-Whitney *U* test was used in SPSS to determine between-group differences. A p-value ≤0.05 was considered significant.

3. Results

62 individuals with COPD who completed the 8-week NMES training program as part of PR were included in the analyses (HF-NMES: n = 33; LF-NMES: n = 29), of whom 48.4% (30 individuals) experienced one or more AECOPD. Generally, patients had severe to very severe COPD and showed clear baseline exercise intolerance (61% with 6MWD ≤350 m; Table 1). There were no significant between-group differences at baseline. The median number of completed sessions in exacerbators vs. non-exacerbators was 75 (73.0–78.0) vs. 78 (73.3–79.0) (p = 0.174; HF-NMES), and 75 (70.0–78.0) vs. 76 (73.8–76.3) (p = 0.947; LF-NMES), respectively (Fig. 1). Over the course of the weeks, the current intensity increased with 22 mA (15–39; HF-NMES) and 26 mA (23–37; LF-NMES) in the exacerbation group and with 27 mA (17–53; HF-NMES) and 36 mA (29–50; LF-NMES) in the non-exacerbation group (p = 0.358 and p = 0.134, respectively). The increase in quadriceps muscle strength and muscle endurance was greater after HF-NMES than after LF-NMES, but there were no significant differences between exacerbators and non-exacerbators within these groups (Fig. 1). The median change in 6MWD in the HF-NMES group was the only significant difference (p = 0.019) between exacerbators (+30 m) and non-exacerbators (+76 m), regarding functional exercise performance.

4. Discussion

This study has shown that the occurrence of mild-to-moderate AECOPD during a NMES training program as part of inpatient PR, does not affect adherence, intensity, and clinical outcomes in severely dyspneic individuals with COPD and quadriceps muscle weakness. These results emphasize that if the clinical status of a patient in whom AECOPD during PR develop permits manageable therapeutic strategies (i.e. antibiotics and/or corticosteroids), maintaining NMES seems a feasible way to potentially counteract exacerbation-related lower-limb muscle dysfunction [20], with HF-NMES being the preferential muscle training modality [14]. The fact that patients made progress following NMES training, irrespective of having AECOPD, is probably due to fast and adequate treatment, as patients are monitored closely when following inpatient PR and facilitating care for acute disease instability in an inpatient setting might increase the likelihood of continuing supervised NMES during AECOPD [21].

The fact that NMES appears to be applicable during AECOPD was already underlined by the *2013 ATS/ERS Statement on Pulmonary*

Table 1
Baseline characteristics.

Variables	Total group		HF-NMES		LF-NMES	
	≥1 AECOPD	0 AECOPD	≥1 AECOPD	0 AECOPD	≥1 AECOPD	0 AECOPD
Number of patients	30	32	19	14	11	18
Age, years	63 (58–68)	65 (60–69)	63 (58–72)	61 (55–66)	63 (58–65)	67 (63–71)
Gender, male (%)	14 (46.7)	15 (46.9)	9 (47.4)	8 (57.1)	5 (45.5)	7 (38.9)
Weight, kg	65.8 (58.0–75.5)	71.4 (62.0–83.0)	67.4 (58.9–75.2)	76.0 (61.7–84.0)	63.4 (55.3–76.5)	71.1 (61.0–81.3)
BMI, kg/m^2	23.6 (20.4–26.8)	25.6 (22.0–30.4)	23.4 (20.2–27.0)	25.4 (21.2–28.0)	23.9 (20.5–26.7)	26.6 (23.0–30.6)
FFMI, kg/m^2	16.3 (14.8–17.0)	16.4 (15.3–17.9)	16.4 (14.8–17.0)	16.3 (14.0–18.5)	16.2 (14.5–16.9)	16.4 (15.7–17.9)
FEV1, % predicted	30 (21–39)	34 (22–41)	33 (20–45)	32 (23–39)	29 (21–32)	36 (22–43)
FEV1/FVC, %	28 (24–35)	29 (23–36)	31 (26–36)	29 (20–36)	24 (23–28)	30 (24–39)
GOLD (I/II/III/IV)	0/3/8/19	0/2/14/16	0/3/6/10	0/2/4/8	0/0/2/9	0/0/10/8
6MWD, m	326 (261–385)*	324 (247–385)!	348 (288–391)*	321 (211–386)	278 (250–385)	346 (271–387)!
Current intensity, mA	31.1 (24.0–41.0)	31.3 (27.6–38.0)	28.1 (24.0–37.5)	29.6 (27.1–34.3)	39.5 (27.5–44.0)	34.0 (26.9–44.6)
CWRT time, s	173 (139–210)^	200 (158–242)&	186 (135–212)$	184 (158–239)#	150 (139–194)*	206 (143–253)#
Quadriceps PT, Nm	70.7 (61.5–89.6)!	73.0 (54.4–104.7)	64.2 (58.9–88.7)!	95.0 (49.5–109.5)	81.8 (69.3–95.3)	63.2 (56.9–86.2)
Quadriceps Total work, J	1120 (799–1394)!	1175 (693–1647)	1070 (692–1457)!	1430 (602–1993)	1211 (1066–1254)	1117 (706–1466)

Variables are presented as median (Interquartile range), unless stated otherwise. ! = 1 missing, * = 2 missing, $ = 3 missing, # = 4 missing, ^ = 5 missing, & = 8 missing.

Abbreviations: HF-NMES, high frequency neuromuscular electrical stimulation; LF-NMES, low frequency neuromuscular electrical stimulation; AECOPD, acute exacerbations of chronic obstructive pulmonary disease; BMI, body mass index; FFMI, Fat Free Mass Index; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; 6MWD, 6-min walking distance; CWRT, constant work-rate test; PT, peak-torque; kg, kilograms; m, meters; mA, milliampere; s, seconds; Nm, Newton-meter; J, Joules.

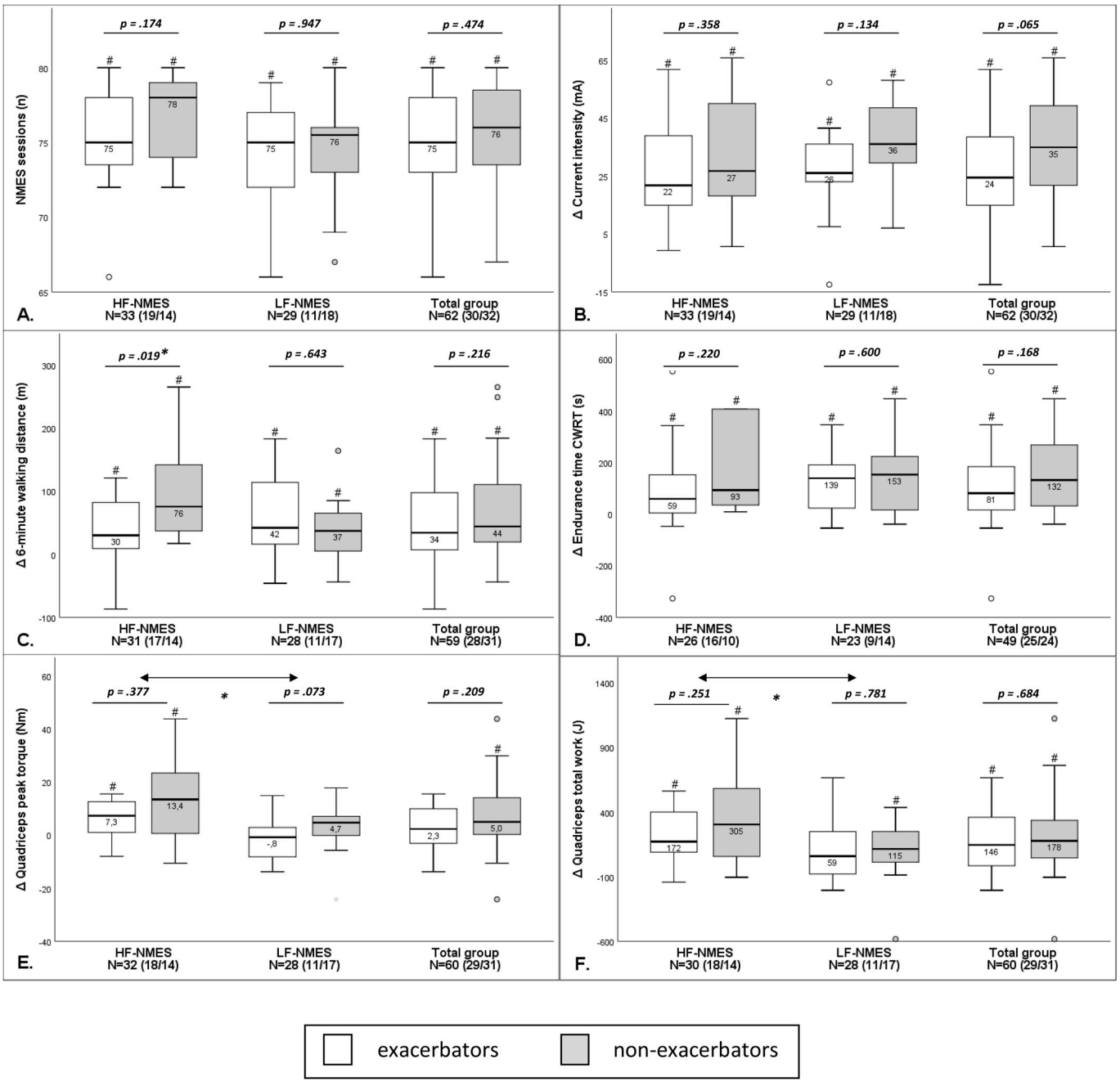

Fig. 1. Differences in NMES outcomes between patients who experienced ≥1 exacerbations (white boxes) and patients who experienced 0 exacerbations (grey boxes). Box plots express total number of NMES sessions (A), changes in current intensity (B), changes in 6-min walking distance (C), changes in endurance time of the CWRT (D), changes in isokinetic peak torque of the quadriceps muscle (E), changes in isokinetic total work of the quadriceps muscle (F), between the start and the end of the 8-week NMES program (as part of inpatient pulmonary rehabilitation). Standard box plots with medians (interquartile ranges) are portrayed, with error bars representing confidence intervals. N = Number of patients within each group (split up in exacerbators/non-exacerbators). NMES, Neuromuscular Electrical Stimulation; HF, high frequency; LF, low frequency; mA, milliampere; m, meters; CWRT, Constant Work-Rate Test; s, seconds; Nm, Newton-meter; J, Joules. # = $p \leq 0.05$ compared with baseline. * = $p \leq 0.05$.

Rehabilitation [22]. However, this statement was primarily based on limited research with very small sample sizes and/or a limited amount of training sessions [9,11]. As far as we know, this is the first study verifying this statement in a considerable number of patients with advanced COPD and quadriceps weakness at baseline. However, we acknowledge that the sample size limits the statistical power of the study to detect statistically significant differences and that the generalizability of our findings is restricted as the DICES sample consisted of severely dyspneic individuals with COPD and quadriceps weakness. Nevertheless, as exacerbations become more frequent as severity of COPD increases [23], the susceptibility of AECOPD may increase when enrolling severely dyspneic patients in PR. Indeed, the amount of mild-to-moderate AECOPD during PR was higher (48.4%) than in other trials [3,24]. Another limitation is the lack of properly documenting the exact timing and duration of AECOPD during the 8-week program, two variables that could have been taken into account in the analyses of the current study. Future research should focus on NMES applied in a larger population of unstable COPD patients, with a complete characterization of exacerbations and a thorough assessment of metabolic and/or structural changes in the lower-limb muscles following HF-NMES. In conclusion, severely

dyspneic individuals with COPD are able to continue and progressively increase their NMES training program during inpatient PR, even in the presence of mild-to-moderate AECOPD, resulting in an increase in quadriceps muscle strength and functional exercise performance.

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Author contributions

RM: Conceptualization, Methodology, Formal analysis, Writing - Original Draft, Visualization. **MJS:** Conceptualization, Investigation, Writing - Review & Editing, Project administration. **FMEF:** Conceptualization, Writing - Review & Editing, Supervision. **AAFS:** Writing - Review & Editing. **EFMW:** Writing - Review & Editing, Funding acquisition. **HWHH:** Writing - Review & Editing. **BB**: Writing - Review & Editing. **PHK:** Writing - Review & Editing. **MAS:** Conceptualization, Writing - Review & Editing, Supervision, Funding acquisition.

Declaration of competing interest

FMEF reports grants and personal fees from AstraZeneca, personal fees from Boehringer Ingelheim, personal fees from Chiesi, personal fees from GlaxoSmithKline, grants and personal fees from Novartis, personal fees from TEVA, outside the submitted work; MAS reports grants from Lung Foundation Netherlands, during the conduct of the main study; EFMW reports grants from the Weijerhorst foundation Netherlands, during the conduct of the main study. RM, MJS, AAFS, HWHH, BB and PHK have nothing to disclose.

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References

[1] GOLD, Global Strategy for the Diagnosis, Management, and Prevention of Chronic, Obstructive Pulmonary Disease, 2019 report. [Accessed 21-09-2019]; Available from: www.goldcopd.com.
[2] C. Burtin, et al., Rehabilitation and acute exacerbations, Eur. Respir. J. 38 (3) (2011) 702.
[3] D.C.W. Braeken, et al., Impact of exacerbations on adherence and outcomes of pulmonary rehabilitation in patients with COPD, Respirology 22 (5) (2017) 942–949.
[4] F. Pitta, et al., Physical activity and hospitalization for exacerbation of COPD, Chest 129 (3) (2006) 536–544.
[5] M.A. Spruit, et al., Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I, Thorax 58 (9) (2003) 752–756.
[6] F. Maltais, et al., Intensity of training and physiologic adaptation in patients with chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 155 (2) (1997) 555–561.
[7] M.J. Sillen, et al., Oxygen uptake, ventilation, and symptoms during low-frequency versus high-frequency NMES in COPD: a pilot study, Lung 189 (1) (2011) 21–26.
[8] M.J. Sillen, et al., Metabolic load during strength training or NMES in individuals with COPD: results from the DICES trial, BMC Pulm. Med. 14 (2014) 146.
[9] A. Abdellaoui, et al., Skeletal muscle effects of electrostimulation after COPD exacerbation: a pilot study, Eur. Respir. J. 38 (4) (2011) 781–788.
[10] S. Giavedoni, et al., Neuromuscular electrical stimulation prevents muscle function deterioration in exacerbated COPD: a pilot study, Respir. Med. 106 (10) (2012) 1429–1434.
[11] J.A. Neder, et al., Home based neuromuscular electrical stimulation as a new rehabilitative strategy for severely disabled patients with chronic obstructive pulmonary disease (COPD), Thorax 57 (4) (2002) 333–337.
[12] WMA, World medical association declaration of Helsinki: ethical principles for medical research involving human SubjectsWorld medical association declaration of Helsinki special communication, J. Am. Med. Assoc. 310 (20) (2013) 2191–2194.
[13] M.J. Sillen, et al., Heterogeneity in clinical characteristics and co-morbidities in dyspneic individuals with COPD GOLD D: findings of the DICES trial, Respir. Med. 107 (8) (2013) 1186–1194.
[14] M.J. Sillen, et al., Efficacy of lower-limb muscle training modalities in severely dyspnoeic individuals with COPD and quadriceps muscle weakness: results from the DICES trial, Thorax 69 (6) (2014) 525–531.
[15] O. Borges, Isometric and isokinetic knee extension and flexion torque in men and women aged 20-70, Scand. J. Rehabil. Med. 21 (1) (1989) 45–53.
[16] J.R. Moon, et al., Tracking fat-free mass changes in elderly men and women using single-frequency bioimpedance and dual-energy X-ray absorptiometry: a four-compartment model comparison, Eur. J. Clin. Nutr. 67 (Suppl 1) (2013) S40–S46.
[17] F.M. Franssen, et al., Limb muscle dysfunction in COPD: effects of muscle wasting and exercise training, Med. Sci. Sport. Exerc. 37 (1) (2005) 2–9.
[18] A.E. Holland, M.A. Spruit, S.J. Singh, How to carry out a field walking test in chronic respiratory disease, Breathe (Sheff) 11 (2) (2015) 128–139.
[19] A. van 't Hul, R. Gosselink, G. Kwakkel, Constant-load cycle endurance performance: test-retest reliability and validity in patients with COPD, J Cardiopulm Rehabil 23 (2) (2003) 143–150.
[20] R.M. Abdulai, et al., Deterioration of limb muscle function during acute exacerbation of chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 197 (4) (2018) 433–449.
[21] M.A. Puhan, et al., Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease, Cochrane Database Syst. Rev. 12 (2016) Cd005305.
[22] M.A. Spruit, et al., An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation, Am. J. Respir. Crit. Care Med. 188 (8) (2013) e13–64.
[23] J.R. Hurst, et al., Susceptibility to exacerbation in chronic obstructive pulmonary disease, N. Engl. J. Med. 363 (12) (2010) 1128–1138.
[24] B.G. Steele, et al., The impact of chronic obstructive pulmonary disease exacerbation on pulmonary rehabilitation participation and functional outcomes, J Cardiopulm Rehabil Prev 30 (1) (2010) 53–60.