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Running head: In-Exsufflation Pressure Titration

Peak Cough Flow Fails to Detect Upper Airway Collapse during Negative Pressure

Titration for Cough-Assist

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Clinical Trial Registration: ClinicalTrials.gov [#NCT02137304]

1 **ABSTRACT**

2 **Objective:** To study the ability of peak cough flow (PCF) and effective cough volume (ECV),
3 defined as the volume exsufflated above 3 L/s, to detect upper airway collapse (UAC) during
4 mechanical insufflation-exsufflation (MI-E) titration in neuromuscular patients.

5 **Design:** Prospective observational study

6 **Setting:** Rehabilitation hospital

7 **Participants:** Twenty-seven patients with neuromuscular disease causing significant impairment
8 of chest wall and/or diaphragmatic movement.

9 **Interventions:** The lowest insufflation pressure producing the highest inspiratory capacity was
10 used. Exsufflation pressure was decreased from -20 cmH₂O to -60/-70 cmH₂O, in 10-cmH₂O
11 decrements, until UAC was detected using the reference standard of flow-volume curve analysis
12 (after PCF, abrupt flattening or flow-rate decrease versus previous less negative exsufflation
13 pressure).

14 **Main outcomes:** Peak cough flow and ECV profiles during expiration with MI-E.

15 **Results:** Upper airway collapse occurred in 10 patients during titration. ECV increased with
16 decreasing expiratory pressure then decreased upon UAC occurrence. PCF continued to increase
17 after UAC occurrence. In 5 other patients, UAC occurred at the initial -20 cmH₂O exsufflation
18 pressure and, during titration, PCF increased and ECV remained unchanged at less than 200 mL.
19 PCF had 0% sensitivity for UAC, whereas ECV had 100% sensitivity and specificity.

20 **Conclusion:** Of 27 patients, 15 experienced UAC during MI-E titration. UAC was associated
21 with an ECV decrease or plateau and with increasing PCF. Accordingly ECV, but not PCF, can
22 detect UAC.

23

24 **Keywords:** cough, mechanical insufflation-exsufflation, neuromuscular disease, exsufflation,
25 upper airway collapse

26

27

28 **List of abbreviations:**

29 ECV : effective cough volume

30 MEP: maximum expiratory pressure

31 MI-E: mechanical insufflation-exsufflation

32 MIP: maximum inspiratory pressure

33 NMD: neuromuscular disease

34 OSA: obstructive sleep apnea

35 PCF: peak cough flow

36 UAC: upper airway collapse

37 VC: vital capacity

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44 INTRODUCTION

45

46 Poor cough efficiency resulting in an inability to clear the airways of secretions is a major
47 risk factor for acute respiratory failure in patients with neuromuscular disease (NMD).^{1,2} Cough-
48 assistance methods include manual and mechanical techniques providing inspiratory and/or
49 expiratory assistance to improve cough efficiency, mobilize and clear the airway secretions, and
50 avoid complications associated with secretion retention.¹⁻⁶ Peak cough flow (PCF) is usually
51 taken as the criterion for determining that airway clearance is effective, the cut-off being 160-180
52 L/min in adults with NMD.⁷⁻¹³ A baseline PCF<180 L/min (3L/s) is required for reimbursement
53 of secretion-clearance devices by the statutory health insurance systems in Belgium¹⁴ and
54 France.¹¹ Rather than to use a PCF threshold U.S. health insurance companies prefer a clinical
55 evaluation and criteria for MI-E devices (E0482) covering are : 1) a neuromuscular disease (refer
56 to the 10th revision of the “International Statistical Classification of Diseases and Related Health
57 Problems“), and 2) this condition is causing a significant impairment of chest wall and/or
58 diaphragmatic movement, resulting in an inability to clear retained secretions.

59 Peak cough flow is also the most widely used parameter for assessing the performance of
60 cough-assist techniques in patients with NMD.^{8, 15, 16} Mechanical insufflation-exsufflation (MI-E)
61 is currently considered the technique of choice for the weakest patients with NMD.⁶ The
62 insufflation pressure that achieves the highest PCF is viewed as optimal and is lower than the
63 value providing maximal insufflation.¹⁷ It has been suggested that the optimal exsufflation
64 pressure can also be defined as the value achieving the highest PCF. However, PCF measurement
65 may fail to detect upper airway collapse (UAC) caused by the application of negative pressure.
66 UAC may impair cough effectiveness according to two studies showing evidence of upper airway

67 obstruction during MI-E.^{18, 19} However, the techniques used in these studies^{18, 19} are not readily
68 applicable to exsufflation pressure titration in everyday practice.

69 We hypothesized that, when upper airway collapse occurs during titration, the
70 exsufflation pressure achieving the highest volume exhaled at an efficient flow [i.e. above 3
71 L/min], designated as “effective cough volume” (ECV), is systematically higher (i.e. less
72 negative) than the exsufflation pressure achieving the highest PCF value. The objective of this
73 prospective study in patients with severe respiratory muscle weakness due to NMD was to
74 investigate changes in PCF and ECV during MI-E, particularly upon the occurrence of UAC, as
75 detected by analysis of the flow-volume curve. The performance of PCF and ECV in detecting
76 UAC was quantified.

77

78 MATERIAL AND METHODS

79

80 Patients

81 This observational study was approved by the French national ethics committee and
82 registered on ClinicalTrials.gov (#NCT02137304). In 2016 and 2017, we enrolled 27 patients
83 with NMD during their annual follow-up visits to the post-intensive care unit, which routinely
84 included patient education about cough-assist techniques. All 27 patients met the French,
85 Belgium and US criteria required for MI-E coverage. At each visit, the following parameters
86 were recorded: vital capacity (VC),²⁰ unassisted PCF,²⁰ maximum expiratory pressure (MEP),
87 and maximum inspiratory pressure (MIP).^{21, 22} Inclusion criteria were documented NMD, reason
88 for using MI-E, age >18 years, hemodynamic stability, absence of acute bronchial congestion
89 (respiratory tract infection) in the past month, and PCF lower than 4.5 L/s.⁵ Patients gave written
90 informed consent before study inclusion.

91 **Study protocol**

92 Mechanical insufflation-exsufflation was performed using a facemask [Ambu UltraSeal,
93 Ambu, Bordeaux, France] and the Cough-Assist E70 device [JH Emerson Co., Cambridge, MA,
94 USA]. Measurements during maneuvers were obtained with a spirometer (Micro 6000
95 spirometers; Medisoft, Sorinnes, Belgium) connected to the MI-E circuit and were performed
96 with the study participants seated comfortably in their adapted wheelchair; the experiment was
97 started after a period of quiet breathing. Patients were seated in their own electric wheelchair.
98 Postural adjustments were made following patients' advice for their best respiratory comfort.
99 Degree of tilt, recline or elevation of leg rests were not measured. If possible, the degrees of tilt
100 and recline tried to allow the patient having an overall view on Cough-Assist E70 screen in order
101 to get a visual feedback. The head was on the headrests maintained in the neutral position, when
102 it was possible for the patient, to avoid bias due to effects of position on deep breathing and
103 coughing. Throughout the tests, oxygen saturation and heart rate were monitored using pulse
104 oximetry.

105 The day before testing, the patients were familiarised with the study cough-assist
106 techniques. The optimal insufflation pressure was determined by starting at 10 cmH₂O,
107 increasing in 5 cmH₂O steps up to 20 cmH₂O, and finally increasing further in 2 cmH₂O steps to
108 a maximum of 40 cmH₂O. Measurements were performed two or three times at each pressure
109 level. The individual pressure titration was stopped when further increase did not lead to
110 additional improvement or if patients did not tolerate higher pressures.¹⁷ Insufflation poor
111 tolerance was defined as an overinflation sensation hindering the compression phase of cough.

112
113 Expiratory pressure was titrated on the next day. Three physiotherapists (ML, AB, and
114 LDAC) carried out the MI-E trials. Two physiotherapists participated in each trial: one used the

115 MI-E device and the other performed the measurements. Great care was taken to avoid leaks
116 around the mask during MI-E. The physiotherapists stimulated the patient's efforts to cough via
117 strong verbal encouragement. MI-E was delivered via a facemask (Ambu UltraSeal^b) using the
118 Cough-Assist E70^c device in automatic mode, as operator-bias might have occurred in manual
119 mode. The duration of insufflation-exsufflation was set at 2.5 s. The optimal insufflation pressure
120 determined on the previous day was used. Exsufflation pressure titration was performed starting
121 at -20 cmH₂O then decreasing in 10 cmH₂O steps to -60 cmH₂O. For those patients expressing
122 the wish to test the limits of the device, the exsufflation pressure was further decreased up to -70
123 cmH₂O. Each exsufflation pressure was tested at least three times,²³ and the best flow-volume
124 curve was retained for the analysis, which included determination of the highest volume
125 exsufflated at a flow greater than 3L/s (see below).

126 Individual exsufflation pressure titration was stopped when a further decrease was poorly
127 tolerated by the patient or when an alteration in the flow-volume curve suggested UAC.
128 Exsufflation poor tolerance was defined as an upper airway irritation and/or an UAC sensation
129 limiting expiration and/or a dyspnea increase and/or a desynchronization between the patient and
130 the cough device assistance. Flow-volume curve was considered altered by the physiotherapists
131 on the basis of studies previously described with the negative expiratory pressure technique used
132 to assess upper airway collapsibility during spontaneous breathing to identify patients at risk for
133 obstructive sleep apnea (OSA)²⁴. The spirometer used for the study automatically superimposed
134 successive flow-volume curves (Figure 1). A flow rate decrease occurring abruptly after PCF
135 measurement on at least part of the exhaled volume, compared to the flow rate observed at the
136 previous titration step, was thus taken to indicate UAC. In addition, abrupt flow-volume curve
137 flattening at the beginning of MI-E titration (i.e., at the highest negative exsufflation pressure of -
138 20 cmH₂O) is very typical to UAC but does not allow for comparison to a previous flow-volume

139 curve. Consequently, in this situation, UAC was diagnosed if further decreasing the negative
140 exsufflation pressure failed to improve the appearance of the flow-volume curve.

141 The UAC determination by flow-volume curve analysis was checked later by two
142 respiratory physiologists (FL and HP).

143 Patients could rest between each tested pressure level, and total patient participation did
144 not exceed 40 minutes.

145

146 **Statistical analysis**

147 Baseline and anthropometric data were described as number (%) for categorical variables,
148 mean \pm SD for normally distributed continuous variables, and median [interquartile range] for
149 skewed continuous variables. Inter-observer reliability of UAC detection based on the flow-
150 volume curve appearance was assessed using Cohen's kappa (κ) statistics. Sensitivity and
151 specificity of PCF and ECV for identifying UAC at the same negative exsufflation pressure
152 during MI-E titration were calculated. A segmented linear mixed-effects regression model was
153 built to assess changes in pressure over flow.

154 Patients were categorized based on their flow-volume curve patterns. Comparisons across
155 patient categories of relied on ANOVA for normally distributed and homoscedastic quantitative
156 variables and on the Kruskal-Wallis test for non-normally distributed or probably non-
157 homoscedastic quantitative variables. Qualitative variables were compared across patient
158 categories by applying the Mantel-Haenszel chi-square test or, when sample size was <5 , Fisher's
159 exact test.

160 All tests were two-tailed and P values <0.05 were taken to indicate significant differences.

161 The statistical analyses were carried out with R software version 2.2.0.²⁵

162

163 **RESULTS**

164

165 We included 27 patients with advanced muscle weakness due to NMD. Table 1 lists their
166 main characteristics.

167

168 **Flow-volume curve analysis**

169 Among the 27 patients, 15 exhibited flow-volume curve evidence of UAC during MI-E.
170 For all 15 patients, both observers agreed that the flow-volume curve profile indicated UAC
171 (Cohen's $\kappa=1$).

172 The changes in flow-volume curve according to exsufflation pressure allowed us to divide
173 the patients into three groups. Figure 2 and Table 2 showed individual characteristics of these 3
174 groups:

175 - profile A group [Figure 2, patient #3; Table 2] : In 12 patients, flow-volume curve area
176 improved quasi-systematically as the exsufflation pressure decreased from -20 to -60 or -70
177 cmH₂O indicating that no UAC occurred. Of these 12 patients, 4 asked to test the -70 cmH₂O
178 exsufflation pressure.

179 - profile B group [Figure 2, patient #13; Table 2] : In 10 patients, and flow-volume curve
180 improved as the exsufflation pressure decreased, until UAC occurred and induced, after the peak
181 flow, an abnormal abrupt fall in expiratory flow, which was confirmed when comparing these
182 flow-volume loop with those obtained with the previous and less negative exsufflation pressure
183 [profile B in Figure 2]. The exsufflation pressure at which UAC occurred was -70 cmH₂O in 1
184 patient, -60 cmH₂O in 7 patients, and -50 cmH₂O in 2 patients (Table 2). In one patient, a

185 decrease in the tolerance characterized by an uninterrupted irritating cough occurred at -50
186 cmH₂O and was concomitant with occurrence of UAC (patient #8 in Table 2).

187 - profile C group [Figure 2, patient #17; Table 2]: For the 5 remaining patients, UAC
188 occurred at the beginning of titration. Accordingly the flow-volume curve flattened abruptly
189 starting at the step that immediately followed the initial -20 cmH₂O exsufflation pressure value
190 and did not improve when decreasing expiratory pressure. In 3 patients, titration was stopped
191 before reaching -60 cmH₂O, at -50 cmH₂O in 1 patient and -40 cmH₂O in 2 patients, because of a
192 decrease in the tolerance characterized by clinical sensation of upper airway collapse.

193

194 **Peak cough flow (PCF)**

195 PCF consistently increased with decreasing exsufflation pressure, regardless of whether
196 UAC did or did not occur. Thus, PCF was always highest at the lowest exsufflation pressure
197 tested. As shown in Figure 3, PCF increased steadily by about 0.32 L/s per 10 cmH₂O from the
198 beginning to the end of titration.

199

200 **Effective cough volume (ECV)**

201 In the group with profile A, ECV increased steadily from the beginning to the end of
202 titration. In the group with profile B, ECV increased steadily until UAC occurred then
203 consistently decreased. In the group with profile C, ECV remained stable and below 200 mL as
204 the exsufflation pressure decreased.

205

206 **Comparison between PCF and ECV**

207 The relative changes in PCF and ECV during negative exsufflation pressure titration are
208 reported in Figure 4. In profile A, PCF and ECV increased concomitantly. In profile B, ECV

209 increased initially with PCF, until UAC occurred, after which ECV decreased while PCF
210 continued to increase. In profile C, PCF increased steadily, while ECV remained below 200 mL.
211 Thus, UAC was always accompanied with an increase in PCF contrasting with either a decrease
212 in EVC or, when UAC occurred at the beginning of titration, a stable ECV value below 200 mL.
213 A decrease in ECV versus earlier value had 100% sensitivity and 100% specificity for detecting
214 UAC, whereas a decrease in PCF versus earlier value had 0% sensitivity and 100% specificity.

215

216 **Comparison between patient groups with versus without upper airway collapse (UAC)**

217 When we compared patients with versus without UAC diagnosed based on the flow-
218 volume curve (i.e., those with profile A versus those with profile B or C), we found no significant
219 differences in mechanical ventilation duration, VC, MIP, MEP, or baseline PCF ($P=0.78, 0.32,$
220 $0.58, 0.12,$ and $0.24,$ respectively). The distribution of NMD diagnoses differed significantly
221 across the three flow-volume curve profiles (Fisher's exact test, $P=0.03$), chiefly because UAC
222 occurred during titration in all 4 patients with spinal muscular atrophy.

223

224 **DISCUSSION**

225 We report the first systematic evaluation of flow-volume curve profiles during
226 exsufflation pressure titration for MI-E in patients with NMD. PCF, the parameter generally used
227 to assess cough efficiency, increased consistently as exsufflation pressure decreased. However,
228 despite increasing PCF values, 15 of the 27 patients exhibited flow-volume curve findings
229 indicating UAC and coinciding with a decrease in ECV (defined as the volume coughed at a flow
230 >3 L/s), suggesting impaired cough efficiency. In contrast when the flow-volume curve showed
231 no evidence of UAC, ECV increased steadily as the exsufflation pressure decreased.

232 The maximum flow achievable during forced expiration or coughing started after maximal
233 or submaximal lung inflation is widely believed to be chiefly effort-dependent.²⁶ However, after
234 the early peak flow, if sufficient expiratory effort is produced to cause dynamic compression of
235 the intrathoracic airways, flow becomes effort-independent (i.e., limited): beyond a given driving
236 pressure, additional force generated by the expiratory muscles does not further increase flow,
237 which diminishes progressively from the early peak until the end of the maneuver.²⁶ This flow
238 limitation is explained by the drop in alveolar pressure along the airways that occurs during
239 expiration, due to airway resistance. The airway pressure may become equal to the intrapleural
240 pressure during forced expiration, i.e., may reach the equal pressure point. When the equal
241 pressure point is reached at the level of the trachea or large bronchi, the presence of hyaline
242 cartilage prevents airway collapse.²⁶ However, due to the decrease in lung volume during forced
243 expiration, the alveolar elastic recoil pressure decreases and the equal pressure point moves
244 upstream towards the alveoli. The equal pressure point may then be reached at the thin-walled
245 bronchioles, which may collapse, inducing a typical depression in the flow-volume curve.²⁶ This
246 phenomenon of intrathoracic airway compression and collapse is critical for the secretion
247 clearance mechanism, as it induces increases in linear velocity and kinetic airstream energy,
248 thereby improving the mobilization and expulsion of material from the bronchial tree.²⁶
249 Accordingly, sufficient expiratory muscle force is required to reach the flow-limitation threshold.
250 Thus, the greater is the expiratory effort, the earlier is the flow limitation reached during the
251 forced expiratory maneuver and, therefore, the better is the flow-volume curve.

252 In many patients with NMD, the expiratory muscle weakness limits the production of a
253 satisfactory flow-volume curve. Expiratory muscle weakness does not allow an optimal driving
254 pressure in order to generate a high peak flow and reach the flow-limitation threshold. During the
255 expulsive phase of cough, this weak driving pressure becomes the main cause of expiratory flow

256 reduction. Accordingly, applying negative pressure during expiration assist expiratory muscle
257 weakness and may increase the peak flow or PCF by increasing the driving pressure and may also
258 improve the second part of the expiratory flow-volume curve by reaching the flow-limitation
259 threshold. This effect of negative exsufflation pressure was seen in our patients with profile A.
260 However, as previously demonstrated in a few patients, if negative pressure induces UAC,^{18, 19}
261 adding further flow limitation, then the flow coming from the lungs may be altered from the
262 beginning to the end of the forced expiration. Moreover, airway collapse may be missed if only
263 peak flow or PCF is measured, as these parameters may be paradoxically increased at the mouth
264 when the collapse causes rapid expulsion of the air contained in the upper airway, although the
265 contribution to airway clearance of airflow from the intrathoracic airways may be reduced by the
266 upper airway obstruction. Our results support this possibility: in profile B seen in 10 of the 27
267 patients, PCF continued to increase with decreasing negative exsufflation pressure, but the ECV
268 decreased after a threshold, resulting in a flattening of the subsequent part of the flow-volume
269 curve. These results are also concordant with studies that used the negative expiratory pressure
270 technique to assess upper airway collapsibility, as a mean of identifying patients at risk for
271 OSA.²⁴ This technique consists in applying a slightly negative pressure of -5 to -10 cm H₂O at the
272 mouth at the early expiration phase of quiet tidal breathing and comparing the ensuing FV-C with
273 that observed during a control expiration. Negative expiratory pressure application elicits a flow
274 spike, which can exceed 2.5 L/s during passive exhalation, despite the only slightly negative
275 pressure. This spike is ascribed mainly to dynamic airway compression of the compliant oral and
276 neck structures.²⁴ After the spike, flow decreases to a low value, due to an increase in resistance
277 of the oropharyngeal structures, which reflects upper airway collapsibility (extrathoracic
278 expiratory flow limitation).²⁴ It has been demonstrated that this transient spike in expiratory flow
279 correlates with the severity of OSA.²⁴ Compared to those used for the negative expiratory

280 pressure technique, our conditions of negative pressure application were different: the inspiratory
281 and expiratory efforts during coughing were maximal or submaximal, and the expiratory
282 pressures were considerably lower. Nevertheless, our hypothesis that a high PCF value recorded
283 at the airway opening does not necessarily indicate cough efficiency throughout the bronchial tree
284 is supported by a recent bench study, in which an MI-E device was attached to a lung simulator
285 with and without a collapsible tube.²⁷ PCF values were higher with than without the collapsible
286 tube. The collapsible tube clearly tends to decrease PCF upstream, while increasing PCF
287 downstream due to the additional flow produced by tube wall displacement.

288 In profile C seen in 5 of the 27 patients and characterized by early UAC, ECV remained
289 below 200 mL. A likely explanation is that a major portion of the ECV in this situation was the
290 volume ejected from the collapsing upper airway previously expanded by the insufflation
291 preceding the exsufflation. Previous studies suggest that upper airway volume may be far less
292 than 200 mL.^{28, 29} Insufflation might result in a larger volume, due to upper airway expansion.
293 However, adduction of laryngeal structures during insufflation has been reported.¹⁸ In addition,
294 upper airway narrowing during exsufflation never results in complete obstruction.¹⁹

295 We chose ECV, i.e., the volume exhaled above a flow rate of 3 L/s, to assess cough
296 efficiency. The volume exhaled at flow rates above the threshold usually considered to be
297 efficient during coughing,⁶ i.e., 3 L/s, is relevant. In addition, ECV is easy to determine from
298 flow-volume curves in everyday practice.

299 In our study, the occurrence of suspected UAC during the application of negative
300 exsufflation pressures was not related to the severity of the respiratory muscle dysfunction.
301 However, all 4 patients with spinal muscular atrophy had suspected UAC. This result is not
302 surprising, given that patients with spinal muscular atrophy often exhibit upper airway
303 dysfunction, which may increase the risk of upper airway collapse during MI-E. Thus, studies

304 have established that the decrease in hypopharyngeal cross-section surface area seen during
305 exsufflation in patients with amyotrophic lateral sclerosis was more marked in the subgroup with
306 bulbar symptoms.¹⁸ Upper airway dysfunction may also be prevalent in spinal muscular atrophy,
307 as chewing and swallowing difficulties have been documented in 28% and 25% of patients with
308 type II disease, respectively.³⁰ Unfortunately, because our study was observational we were
309 unable to modify our standard practice of confining the evaluation to spirometry, which is
310 currently viewed as the reference standard for PCF measurement. Therefore, upper airway
311 function was not routinely investigated. Nevertheless, all 5 patients with profile C, characterized
312 by upper airway collapse starting at the first negative pressure level (-20 cmH₂O), including 3 of
313 the 4 patients with spinal muscular atrophy, reported swallowing difficulties consistent with
314 severe upper airway dysfunction. These results strongly support a need for accurately
315 determining the optimal MI-E negative pressure in patients with NMD and inefficient cough,
316 particularly when bulbar symptoms are present. Flow-volume curve analysis can be an efficient
317 tool for achieving this goal.

318

319 **Study Limitations**

320 An important limitation of this study is that performance was evaluated only during
321 spirometry. To date, it is unclear whether PCF, ECV, or the flow-volume curve profile is most
322 important for assessing cough efficiency. Nevertheless, a negative exsufflation pressure that
323 decreases ECV may limit cough efficiency. It may be appropriate to discuss the trade-off between
324 improving PCF and keeping the flow-volume curve unaltered. In addition, when the flow-
325 volume curve profile suggests UAC occurring at the beginning of negative exsufflation pressure
326 titration (profile C), further decreasing the exsufflation pressure is unlikely to be beneficial. Thus,
327 in our patients with profile C, decreasing the exsufflation pressure had little effect on ECV, which

328 remained below 200 mL. Alternative or additional techniques, such as manual assisted coughing,
329 may be beneficial³¹ by increasing airway pressure and possibly preventing UAC during
330 exsufflation, but were not tested in our study. These points should be addressed by future
331 research. In addition, flow-volume curve analysis should be included in guidelines about optimal
332 MI-E titration. We did not test negative exsufflation pressures above -20 cmH₂O, which is the
333 highest initial pressure setting suggested in the literature.¹⁶ Finally, we did not evaluate patient
334 comfort or subjective cough effectiveness. However, in a previous study using various inflation
335 techniques, we found no association of cough performance with subjective impressions.³¹ Finally,
336 patient position may have an important impact on respiratory performances. Postural adjustments
337 were made according to patients' opinion on their best respiratory comfort. We did not describe
338 the position on the wheelchair (degree of tilt, recline or elevating leg rests measures). They might
339 be important to control in future studies.

340

341 **Conclusions**

342 In conclusion, in some patients with NMD, decreasing the negative exsufflation pressure
343 used for MI-E was associated with a decline in the volume exhaled at a flow rate above 3 L/s
344 (ECV), suggesting UAC. This decline in ECV was accompanied with an increase in PCF, which
345 thus failed to detect UAC. Our findings suggest that analysis of the maximal expiratory flow-
346 volume curve, with ECV measurement, may improve the identification of the negative
347 exsufflation pressure associated with maximal cough efficiency.

348

349

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352 **REFERENCES**

- 353
- 354 1. Ambrosino N, Carpenè N, Gherardi M. Chronic respiratory care for neuromuscular
355 diseases in adults. *Eur Respir J* 2009;34(2):444-51.
- 356 2. Benditt JO, Boitano LJ. Pulmonary issues in patients with chronic neuromuscular disease.
357 *Am J Respir Crit Care Med* 2013;187(10):1046-55.
- 358 3. Bach JR. Mechanical insufflation-exsufflation. Comparison of peak expiratory flows with
359 manually assisted and unassisted coughing techniques. *Chest* 1993;104(5):1553-62.
- 360 4. Hull J, Aniapravan R, Chan E, Chatwin M, Forton J, Gallagher J et al. British Thoracic
361 Society guideline for respiratory management of children with neuromuscular weakness. *Thorax*
362 2012;67 Suppl 1:i1-40.
- 363 5. Bott J, Blumenthal S, Buxton M, Ellum S, Falconer C, Garrod R et al. Guidelines for the
364 physiotherapy management of the adult, medical, spontaneously breathing patient. *Thorax*
365 2009;64 Suppl 1:i1-51.
- 366 6. Chatwin M, Toussaint M, Goncalves MR, Sheers N, Mellies U, Gonzales-Bermejo J et al.
367 Airway clearance techniques in neuromuscular disorders: A state of the art review. *Respiratory*
368 *medicine* 2018;136:98-110.
- 369 7. Bach JR, Saporito LR. Criteria for extubation and tracheostomy tube removal for patients
370 with ventilatory failure. A different approach to weaning. *Chest* 1996;110(6):1566-71.
- 371 8. Bach JR, Ishikawa Y, Kim H. Prevention of pulmonary morbidity for patients with
372 Duchenne muscular dystrophy. *Chest* 1997;112(4):1024-8.
- 373 9. Dohna-Schwake C, Ragette R, Teschler H, Voit T, Mellies U. Predictors of severe chest
374 infections in pediatric neuromuscular disorders. *Neuromuscular disorders : NMD*
375 2006;16(5):325-8.
- 376 10. Boitano LJ. Management of airway clearance in neuromuscular disease. *Respiratory care*
377 2006;51(8):913-22; discussion 22-4.
- 378 11. Leger P, Paulus J. [Recommendations of HAS: Practical issues in home non-invasive
379 ventilation in patients with neuromuscular disease]. *Revue des maladies respiratoires* 2006;23(4
380 Suppl):13S141-3.
- 381 12. Rokadia HK, Adams JR, McCarthy K, Aboussouan LS, Mireles-Cabodevila E. Cough
382 Augmentation in a Patient with Neuromuscular Disease. *Annals of the American Thoracic*
383 *Society* 2015;12(12):1888-91.
- 384 13. Sancho J, Servera E, Banuls P, Marin J. Effectiveness of assisted and unassisted cough
385 capacity in amyotrophic lateral sclerosis patients. *Amyotrophic lateral sclerosis & frontotemporal*
386 *degeneration* 2017;18(7-8):498-504.
- 387 14. Toussaint M, Boitano LJ, Gathot V, Steens M, Soudon P. Limits of effective cough-
388 augmentation techniques in patients with neuromuscular disease. *Respiratory care*
389 2009;54(3):359-66.
- 390 15. Suarez AA, Pessolano FA, Monteiro SG, Ferreyra G, Capria ME, Mesa L et al. Peak flow
391 and peak cough flow in the evaluation of expiratory muscle weakness and bulbar impairment in
392 patients with neuromuscular disease. *Am J Phys Med Rehabil* 2002;81(7):506-11.
- 393 16. Morrow B, Zampoli M, van Aswegen H, Argent A. Mechanical insufflation-exsufflation
394 for people with neuromuscular disorders. *The Cochrane database of systematic reviews*
395 2013;12:CD010044.

- 396 17. Mellies U, Goebel C. Optimum insufflation capacity and peak cough flow in
397 neuromuscular disorders. *Annals of the American Thoracic Society* 2014;11(10):1560-8.
- 398 18. Andersen T, Sandnes A, Brekka AK, Hilland M, Clemm H, Fondenes O et al. Laryngeal
399 response patterns influence the efficacy of mechanical assisted cough in amyotrophic lateral
400 sclerosis. *Thorax* 2017;72(3):221-9.
- 401 19. Sancho J, Servera E, Diaz J, Marin J. Efficacy of mechanical insufflation-exsufflation in
402 medically stable patients with amyotrophic lateral sclerosis. *Chest* 2004;125(4):1400-5.
- 403 20. Standardized lung function testing. Official statement of the European Respiratory
404 Society. *Eur Respir J* 1993;16 Suppl:1-100.
- 405 21. Hart N, Polkey MI, Sharshar T, Falaize L, Fauroux B, Raphael JC et al. Limitations of
406 sniff nasal pressure in patients with severe neuromuscular weakness. *Journal of neurology,*
407 *neurosurgery, and psychiatry* 2003;74(12):1685-7.
- 408 22. Trebbia G, Lacombe M, Fermanian C, Falaize L, Lejaille M, Louis A et al. Cough
409 determinants in patients with neuromuscular disease. *Respiratory physiology & neurobiology*
410 2005;146(2-3):291-300.
- 411 23. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A et al.
412 Standardisation of spirometry. *Eur Respir J* 2005;26(2):319-38.
- 413 24. Insalaco G, Romano S, Marrone O, Salvaggio A, Bonsignore G. A new method of
414 negative expiratory pressure test analysis detecting upper airway flow limitation to reveal
415 obstructive sleep apnea. *Chest* 2005;128(4):2159-65.
- 416 25. R Development Core Team. R: A Language and Environment for Statistical Computing
417 n.d. [cited 2019 June 3rd]. Available from: URL: <http://www.R-project.org>.
- 418 26. Mead J, Turner JM, Macklem PT, Little JB. Significance of the relationship between lung
419 recoil and maximum expiratory flow. *Journal of applied physiology* 1967;22(1):95-108.
- 420 27. Lachal R, Louis B, Subtil F, Guerin C. Bench Assessment of the Effect of a Collapsible
421 Tube on the Efficiency of a Mechanical Insufflation-Exsufflation Device. *Respir Care* 2019.
- 422 28. Chousangsunton K, Bhongmakapat T, Apirakkittikul N, Sungkarat W, Supakul N,
423 Laothamatas J. Upper Airway Areas, Volumes, and Linear Measurements Determined on
424 Computed Tomography During Different Phases of Respiration Predict the Presence of Severe
425 Obstructive Sleep Apnea. *Journal of oral and maxillofacial surgery : official journal of the*
426 *American Association of Oral and Maxillofacial Surgeons* 2018;76(7):1524-31.
- 427 29. Boutet C, Abdirahman Mohamed Moussa S, Celle S, Laurent B, Barthelemy JC, Barral
428 FG et al. Supra-Epiglottic Upper Airway Volume in Elderly Patients with Obstructive Sleep
429 Apnea Hypopnea Syndrome. *PloS one* 2016;11(6):e0157720.
- 430 30. Messina S, Pane M, De Rose P, Vasta I, Sorletti D, Aloysius A et al. Feeding problems
431 and malnutrition in spinal muscular atrophy type II. *Neuromuscular disorders : NMD*
432 2008;18(5):389-93.
- 433 31. Lacombe M, Del Amo Castrillo L, Bore A, Chapeau D, Horvat E, Vaugier I et al.
434 Comparison of three cough-augmentation techniques in neuromuscular patients: mechanical
435 insufflation combined with manually assisted cough, insufflation-exsufflation alone and
436 insufflation-exsufflation combined with manually assisted cough. *Respiration; international*
437 *review of thoracic diseases* 2014;88(3):215-22.
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442 SUPPLIERS

- 443 a. Spirometer: Medisoft, Sorinnes, Belgium
- 444 b. Facemask: Ambu, Bordeaux, France
- 445 c. Mechanical insufflation-exsufflation device: JH Emerson Co., Cambridge, MA, USA

446

447

448 **FIGURE LEGENDS**

449

450 **Figure 1**

451 Example of two flow-volume curves obtained during coughing and two different negative
452 pressure applications. The solid line was obtained at a lower pressure than the dotted line and
453 indicated a flow rate decrease for part of the exhaled volume compared to the dotted line,
454 suggesting transient upper airway collapse (UAC). Cough performance was assessed based on
455 the effective cough volume (ECV), defined as the volume exhaled at a flow rate above 3 L/s (180
456 L/min). See text for details.

457

458 **Figure 2**

459 Examples of each of the three flow-volume curve profiles (A, B, and C) during titration of the
460 negative exsufflation pressure applied during mechanical in-exsufflation.

461 A: No upper airway collapse (UAC) : Peak cough flow (PCF) and the effective cough
462 volume (ECV) increase.

463 B: UAC occurs at a specific exsufflation pressure (in this example at -50 cmH₂O,
464 confirmed at -60 cmH₂O) : PCF increases, ECV decreases.

465 C: UAC is observed at the beginning of pressure titration: PCF increases, ECV remains
466 stable when expiratory pressure decreases.

467 See the results section for more details.

468

469 **Figure 3**

470 Peak cough flow changes according to the level of negative expiratory pressure applied

471

472

473 **Figure 4**

474 Individual relationships between peak cough flow (PCF) and effective cough volume (ECV)
475 during negative exsufflation pressure titration in patients with profile A (left panel, n=12) and in
476 those with profile B or C (right panel, n=15). The three profiles are described in Figure 2 and
477 Table 2.

478

479

Figure 1 :

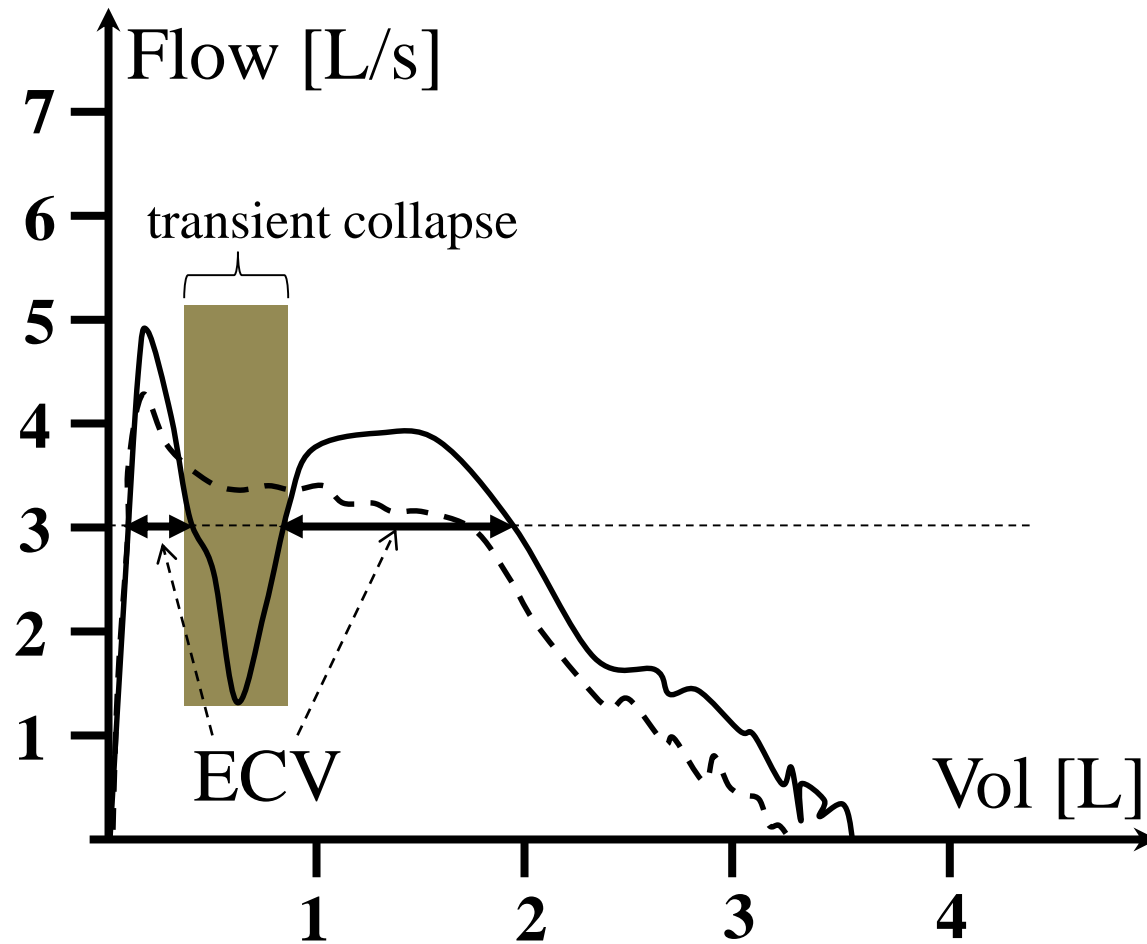


Figure 2 :

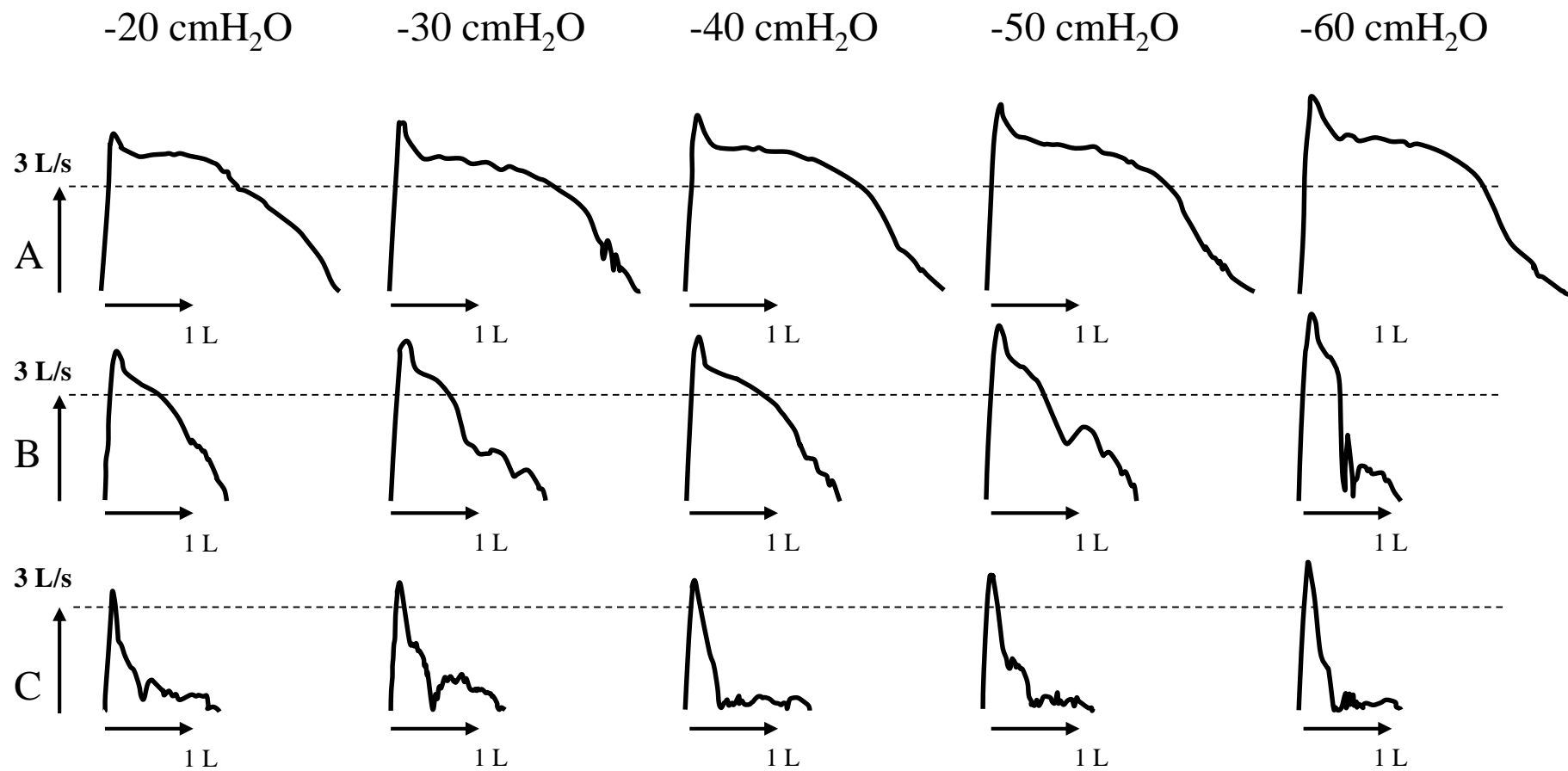


Figure 3 :

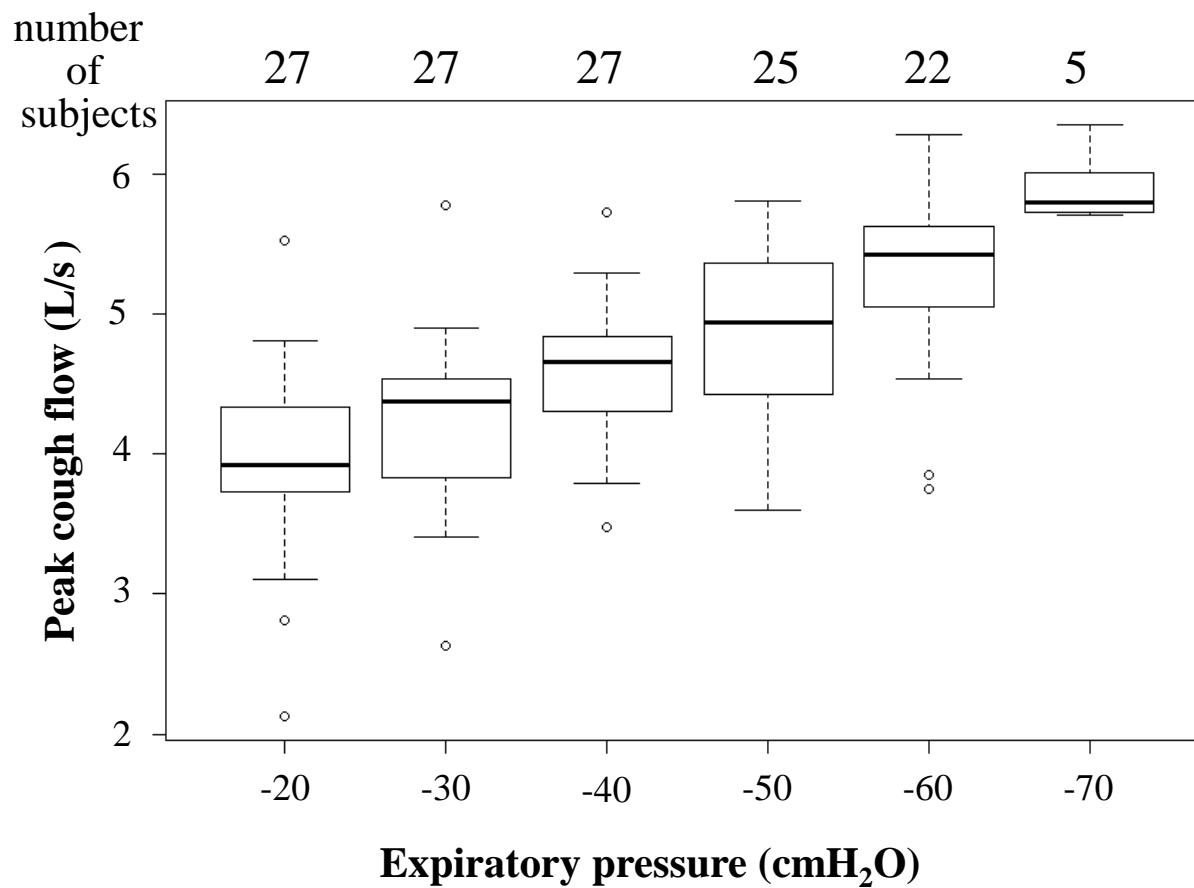


Figure 4 :

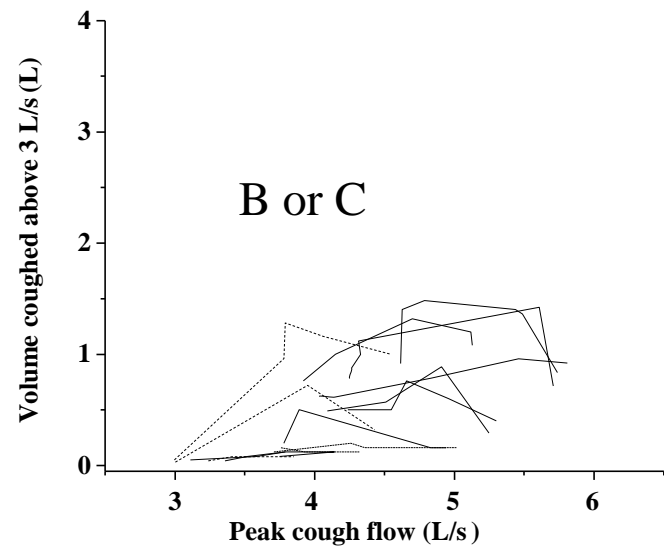
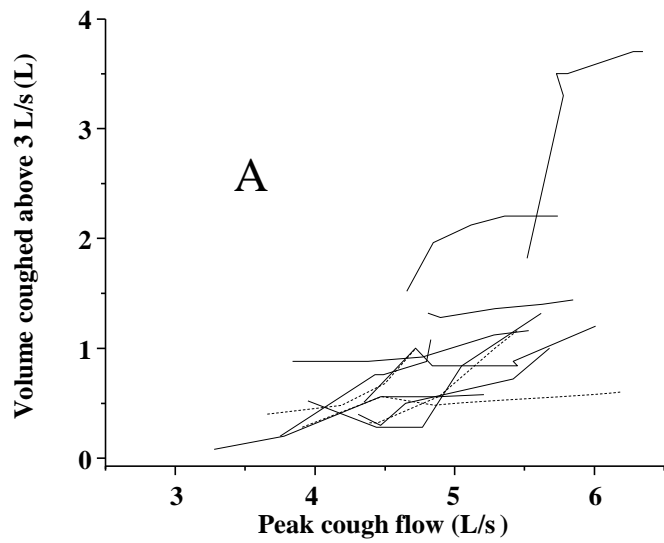


Table 1: Baseline characteristics of the 27 patients with neuromuscular disease

Characteristics	Population n=27
Diagnosis, n (%)	
Duchenne Muscular Dystrophy	14 (51)
Limb Girdle Muscular Dystrophy 2C	4 (15)
Spinal Muscular Atrophy	4 (15)
Limb Girdle Muscular Dystrophy 2D	2 (7)
Congenital Myasthenia Gravis	1 (4%)
Charcot Marie-Tooth	1 (4)
Mitochondrial Myopathy	1 (4)
Age, years	30.6 (\pm 9.2)
Male gender, n (%)	16 (59)
MV duration (hour/day)	10.4 (\pm 5.8)
Upright VC, %	20.2 (\pm 11.8)
MIP, cmH ₂ O	20.3 (\pm 13.9)
MEP, cmH ₂ O	18.2 (\pm 10.7)
PCF, Liter/sec	161.4 (\pm 52.6)

The data are mean \pm SD unless specified otherwise. VC, vital capacity as % of the predicted value according to Quanjer et al.²⁰; PCF, peak cough flow; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; MV, mechanical ventilation

Table 2. Characteristics of the 27 patients with neuromuscular disease and chronic respiratory failure

Profile #	Sex/Age	Diagnosis	MV duration	VC seated	MIP/MEP	PCF	Highest IP/EP tested	PCF/ECV at the highest IP/EP	Best ECV and its EP	
	years		h/day	%	cmH ₂ O	L.min ⁻¹	cmH ₂ O	L.min ⁻¹ / L	L/cmH ₂ O	
A	2	M/22	DMD	8	23	32/23	184	24/-70	381/3.70	3.70/-70
A	3	M/32	LGMD2C	8	16	16/16	135	34/-60	344/2.20	2.20/-60
A	4	F/43	CMT	15	23	11/19	178	34/-70	312/0.58	0.58/-70
A	6	M/20	DMD	24	11	21/15	159	38/-70	361/1.20	1.20/-70
A	9	M/40	LGMD2C	10	12	13/13	107	28/-60	332/1.16	1.16/-60
A	12	M/25	DMD	10	32	25/20	236	24/-70	348/0.96	0.96/-70
A	15	M/21	DMD	8	14	19/21	250	28/-60	337/0.60	0.60/-60
A	22	F/26	LGMD2C	0	36	37/30	239	40/-60	327/1.16	1.16/-60
A	23	M/33	DMD	23	11	8/9	119	34/-60	351/1.44	1.44/-60
A	25	M/22	DMD	12	24	9/9	145	34/-60	290/1.08	1.08/-60
A	26	M/26	DMD	8	17	15/25	195	28/-60	337/1.32	1.32/-60
A	27	F/56	MM	12	52	28/55	227	40/-60	284/1.00	1.00/-60
B	5	M/21	DMD	16	9	11/10	160	34/-60	344/0.92	1.44/-50
B	7	M/23	DMD.	12	17	17/19	203	30/-70	342/0.80	1.50/-60
B	8	M/22	DMD	15	10	13/14	154	36/-50	296/0.16	0.50/-40
B	10	M/27	DMD.	18	8	9/5	128	30/-60	349/0.92	0.96/-50
B	11	F/24	DMD	8	24	13/8	215	34/-60	305/1.32	1.60/-50
B	13	F/38	LGMD2D	8	14	11/11	141	34/-60	318/0.40	0.60/-50
B	16	M/23	DMD	9	13	10/11	187	30/-60	316/0.40	0.60/-50
B	18	F/30	SA	0	50	67/37	220	30/-60	272/1.00	1.16/-50
B	20	F/42	LGMD2C	10	12	9/9	130	24/-60	308/1.08	1.32/-50
B	24	F/44	LGMD2D	10	15	7/10	130	30/-50	266/0.32	0.72/-40
C	1	F/37	SA	0	30	40/27	122	34/-40	227/0.12	0.12/-40
C	14	F/25	DMD	9	14	18/29	142	24/-40	259/0.12	0.12/-40
C	17	M/39	SA	8	12	21/15	69	40/-60	231/0.08	0.08/-60
C	19	F/33	SA	12	12	22/14	104	34/-50	248/0.12	0.12/-50
C	21	F/32	CMS	8	33	46/16	179	28/-60	301/0.16	0.16/-60

Abbreviations: MV, mechanical ventilation; F, female; M, male; VC, vital capacity; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure; PCF, peak cough flow; IP, insufflation pressure; EP, exsufflation pressure; ECV, effective cough volume; DMD, Duchenne muscular dystrophy; SA, spinal muscular atrophy; CMT, Charcot-Marie-Tooth disease; LGMD2C, limb-girdle muscular dystrophy type 2C; LGMD2D, limb-girdle muscular dystrophy type 2D; CMG, congenital myasthenic syndrome; MM, mitochondrial myopathy; A, B, and C profiles, flow-volume profiles depicted in Figure 2