Inspiratory Muscle Training With an Electronic Resistive Loading Device Improves Prolonged Weaning Outcomes in a Randomized Controlled Trial

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OBJECTIVES: To test if the use of an inspiratory muscle training program with an electronic resistive loading device is associated with benefits as to muscle strength, weaning, and survival in the ICU.

DESIGN: Prospective randomized controlled trial.

SETTINGS: Study conducted at the ICU of a Navy's hospital, Rio de Janeiro, Brazil, from January 2016 to September 2018.

PATIENTS: Tracheostomized patients (18–86 yr) on prolonged weaning.

INTERVENTIONS: Participants were assigned to inspiratory muscle training (intervention group) or a traditional T-piece protocol (control group). In the inspiratory muscle training group, participants underwent training with an electronic inspiratory training device (POWERbreathe K-5; Technologies Ltd, Birmingham, United Kingdom).

MEASUREMENTS AND MAIN RESULTS: Changes in respiratory muscle strength and rates of ICU survival and weaning success were compared between groups. Forty-eight participants in the inspiratory muscle training group and 53 ones in the control group were included in the final analysis. The inspiratory muscle training was associated with a substantially higher gain on muscle strength as assessed by the maximal inspiratory pressure (70.5 [51.0–82.5] vs −48.0 cm H_2O [36.0–72.0 cm H_2O]; $p = 0.003$) and the timed inspiratory effort index (1.56 [1.25–2.08] vs 0.99 cm H_2O/s [0.65–1.71 cm H_2O/s]; $p = 0.001$). Outcomes at the 60th day of ICU were significantly better in the intervention group regarding both survival (71.1% vs 48.9%; $p = 0.030$) and weaning success (74.8% vs 44.5%; $p = 0.001$).

CONCLUSIONS : The use of an inspiratory muscle training program with an electronic resistive loading device was associated with substantial muscle strength gain and positive impacts in two very relevant clinical outcomes: the rates of ICU survival and successful weaning.

KEY WORDS: breathing exercises; critical care; mechanical ventilation; rehabilitation; respiratory failure

Mechanical ventilation (MV) can be associated with ventilator-induced diaphragmatic dysfunction (VIDD), preventing the patient's ability to sustain spontaneous ventilation (1–4). It is estimated that about 15% of patients with difficult weaning progress to prolonged weaning (2, 5, 6), resulting in increased hospitalization length, elevated costs, and high mortality rate (7).

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Interventions to restore muscle strength would be of great value in this setting. However, limited data are available, showing that the use of inspiratory muscle training (IMT) can improve both weaning outcomes and survival (8–12).

A recently described weaning predictor, the "timed inspiratory effort" (TIE) index, integrates the maximal inspiratory pressure (PImax) with the time demanded to reach that value. It is calculated as the ratio of the PImax after the first 30 seconds of observation by the time required to reach the PImax whereas keeping the airways occluded with a unidirectional exhalatory valve for up to 60 seconds (6). Such an index has already been safely used to assess the inspiratory muscle strength in two case reports with patients who underwent successful IMT programs (13, 14).

The present study aimed to evaluate the effects of the IMT employing a software-oriented electronic load device on the muscle strength, weaning outcomes, and survival of tracheostomized patients on prolonged weaning using the TIE index values, besides PImax measurements, to assess changes in muscle strength.

METHODS

Design and Settings

Randomized controlled prospective trial enrolling patients with tracheostomy cannula, on prolonged weaning, from 18 to 86 years. Participants were designated into either an IMT (intervention group) or traditional treatment (control group) by lottery by the leader of the nurse shift. It was conducted at the ICU of a Navy's hospital, Rio de Janeiro, Brazil, from January 2016 to September 2018. This study was approved by the local Research Ethics Committee and was registered in "ClinicalTrials.gov" (ID: NCT02932189). Informed consent was obtained from every patient or his next of kin.

Decisions to withdraw participants from the study were taken by the researcher's team. Reasons for withdrawal were recorded and presented in **Supplemental Digital 1** (http://links.lww.com/CCM/G17; **legend**, http://links.lww.com/CCM/G19).

General Procedures

The used ventilator was the model 840TM (Covidien-Nellcor and Puritan Bennett, Boulder, CO); the multivariable monitor, the DX 2010 (Dixtal, São Paulo, Brazil). Immediately before the start of the first T-piece trial, the TIE index and the PImax were obtained for every patient and planned to be repeated every week. Both groups used a protocol of progressively lengthening T-piece trials, re-evaluated daily. In the intervention group, the T-piece trial was preceded by an IMT session as detailed below. The external load of the IMT was planned to be weekly adjusted based on the PImax of the week.

In both groups, the adopted strategy was sustained until patients were successfully weaned. Except when contraindicated, participants underwent early mobilization.

Inclusion and Exclusion Criteria

To be included, patients should conform to the definition of prolonged weaning (5). Participants should have the acute phase of their disease resolved, a cough reflex, and no excessive tracheobronchial secretion. They should have their infection under control, stable cardiovascular status (heart rate ≤ 120 beats/min and systolic blood pressure between 90 and 160 mm Hg, with no or minimal use of vasopressors), hemoglobin greater than 7–10 g/dL, arterial oxygen saturation (Sao_2) greater than 90% with an Fio_2 less than or equal to 0.4 or the ratio of the Po_2 in arterial blood by the Fio_2 greater than or equal to 150 with final positive expiratory pressure less than or equal to 5–8 cm H_2O, respiratory rate less than or equal to 35 breaths/min, supportive pressure less than or equal to 20 cm H_2O, pH greater than 7.30, and temperature less than 38°C (5, 12, 15). The consciousness levels of the included cases were categorized as alert and nonalert.

The exclusion criteria were as follows: use of respiratory depressing sedatives, tracheal stenosis, intracranial pressure greater than 20 mm Hg, severe cardiac insufficiency or hemodynamic instability, and discontinuation of the weaning process due to complications.

T-Piece Protocol

The criteria to interrupt the periods of spontaneous ventilation in T-piece were as follows: agitation/anxiety or depression of the level of consciousness, diaphoresis, dyspnea and or cyanosis, Sao_2 less than 90%, $Paco_2$ greater than 50 mm Hg or increase greater than 8 mm Hg, arterial pH less than 7.33, respiratory rate greater than 35 breaths/min or increase greater than or equal to 50% for greater than or equal to 5 minutes, heart rate greater than 140 beats/min or a sustained

increase greater than 20%, and mean blood pressure greater than 130 mm Hg or less than 70 mm Hg (3, 16).

The participants who demonstrated one or more of these signs during the spontaneous breathing test or within 48 hours after discontinuation of the MV were labeled as weaning failure and returned to ventilatory support (6, 16, 17).

TIE Index and PImax

The TIE index and PImax were recorded using the digital vacuometer MVD 300 (Globalmed, Porto Alegre, Brazil), with a scale of 300 cm H_2O, sensitivity of 1 cm H_2O, and a sampling frequency of 100 ms. A detailed description of the TIE index measurement can be found elsewhere (3, 6, 13, 14). Briefly, before testing, all subjects were ventilated under pressure-support mode. The subjects were positioned in dorsal decubitus with the head elevated at 45°, and the tracheostomy cuff was inflated to prevent leakage during the measurement. After tracheal aspiration, the subjects remained connected to the mechanical ventilator with a 100% FIO_2 for 2 minutes, aiming at preventing hypoxemia during the measurements (3, 6). Then, the mechanical ventilator was disconnected, and the digital vacuometer was coupled to the tracheostomy cannula at the end of a normal expiration (at the level of functional residual capacity). The inspiratory pressures, in cm H_2O, and their corresponding registration time points, in seconds, were stored and analyzed. The TIE index was calculated as the ratio of the PImax registered after the first 30 seconds of observation by the corresponding time to reach it whereas keeping the airways occluded with a unidirectional valve for up to 60 seconds (3, 6). Subjects were not coached for the maneuver that allowed simultaneous determination of the TIE index and PImax. In previous studies, less than 5% of the patients demanded testing interruption and promptly recovered without any consequence after recoupling to MV (3, 6, 13, 14).

For each patient, the TIE index and PImax were measured at the beginning of the weaning process and repeated on a 7 days base. The last measurement was obtained in the week before ventilatory independence, death, or end of the follow-up.

IMT Sessions

The IMT was conducted once daily, between 08:00 and 11:00 AM, from Monday to Friday, as depicted in **Figure 1**. Participants underwent training with a POWER breathe K-5 (Technologies Ltd, Birmingham, United Kingdom) electronic inspiratory training device. Positioning and procedures were the same adopted for the TIE measurement (6). An explanation was given even if the patient was not alert. Vital variables were recorded throughout every session of IMT. Participants were instructed to perform fast and forceful inspirations against the inspiratory resistance to achieve a full inspiration and expiration at every breath. Instructions and encouragements during the sessions were standardized.

The performances of the alert and nonalert participants were accompanied by the layout changes in the screen of the used software (BreatheLink; Power Breathe International, United Kingdom). The training sessions were stopped following the same criteria used for the interruptions of the T-piece trials.

At the end of each training session, patients were returned to MV in pressure-supported ventilation mode for 2 hours to rest. Afterwards, they underwent a T-piece trial, whose length was intended to be increased in each training session. The value of the target load for the IMT was adjusted every 7 days based on the current PImax of each patient.

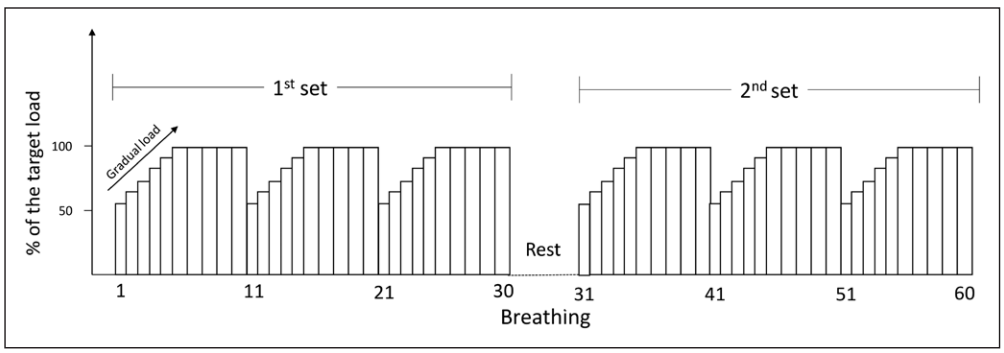

Figure 1. The inspiratory load protocol consisted of imposing an inspiratory load for 60 breaths in 2 sets of 30 breaths each, with a resting period of 2–3 min between sets. Each set comprised of three subsets of 10 breaths each. In each subset of 10 breaths, the load was started at half of the target (set at 40% of the maximal inspiratory pressure of the patient) and progressively escalated until the target load was reached. The last five breaths of each subset were run under the target load.

Definitions

The primary endpoint measure of the study was successful weaning. Survival rate whereas in the ICU was the next to the primary endpoint. Other variables, such as weaning time days, changes in the TIE index, and the PImax values, were also registered.

Prolonged weaning was applied to patients who failed at least three weaning attempts or required greater than 7 days of weaning after the first spontaneous breath test (5). Following the consensus definition, which prevailed by the time of the study design, weaning was considered successful if spontaneous breathing was sustained for greater than or equal to 48 hours after withdrawal from MV (5).

Alertness was defined by real actions such as opening eyes in response to a voice, following simple commands, and or having a Richmond Agitation-Sedation Scale score of –1 to +1 (18).

Time to weaning success was counted from the start of the MV discontinuation until the effective weaning was consolidated. Death in ICU was computed irrespective of the situation of the participant regarding MV dependence.

The posttraining point was defined as the last day of training before the successful weaning.

Statistical Analysis

Based on a previous study (15), it was assumed that the intervention could generate a difference of 30% between groups regarding the primary endpoint (successful weaning). With a type I error of 0.05 and a power of 80%, 80 patients (40 in each group) should be enrolled. Taking a 30% loss to follow-up in consideration, the minimum required sample size at the entrance would be 104 participants.

An analysis was performed to compare weaning success between groups in a way that patients allocated to palliative care along the study, transferred to another unit, and the ones who had the acceptance to participate in the study withdrew by the family were not included.

Kolmogorov-Smirnov test was used to assess the distribution pattern of the variables. Results were expressed as mean and SD for normal distribution or median and internal quartiles otherwise. Differences between continuous variables were examined with the two-tailed *t* test for Gaussian distribution or by the Mann-Whitney *U* test, alternatively. Categorical variables were expressed as frequencies, and differences between them assessed by chi-square or Fisher exact test. Kaplan-Meier curves with log-rank tests were used to compare the time with successful weaning and rates of deaths in both study groups. A Cox proportional hazards model was furthermore used to test for association of IMT with weaning success adjusted for potential confounding factors selected on clinical grounds.

Statistical significance was set at *p* value of less than 0.05. Statistics were performed using SPSS software Version 18.0 for Windows (Armonk, NY).

RESULTS

Three-hundred thirty-three subjects were assessed for eligibility. After applying the exclusion criteria, 110 were randomized, 55 participants in each group. Along with the study, there were nine dropouts, seven in the intervention group and two in control one. The final analysis was performed with 58 and 53 participants in the intervention and control groups, respectively. A flow chart of the entire study period is shown in the **Supplemental Digital 2** (http://links.lww.com/CCM/G18; legend, http://links.lww.com/CCM/G19).

The characteristics of the 101 participants in the study are presented in **Table 1**. Statistically significant differences were found for the frequency of alertness in favor of the intervention group (62% vs 30%; $p = 0.001$). The median initial and final loads applied in the IMT protocol were 17.5 cm H_2O (3.0–40.0 cm H_2O) and 38.5 cm H_2O (17.0–86.0 cm H_2O), respectively, *p* value of less than 0.001 (data not on the table).

Values for selected variables in the intervention and control groups are in **Table 2**. Participants of the intervention group tended to have a longer period of MV before randomization, but statistical significance was not found, *p* equals to 0.256. The IMT was associated with a significant gain in muscle strength as demonstrated by the statistically significant differences in the median values of the TIE index and PImax at the end of follow-up or prior to either successful weaning or death on MV in comparison with initial values ($p = 0.001$ and $p = 0.003$, respectively), both in favor of the intervention group. The frequency of two or more interruptions during the weaning trial was higher in the control group ($p = 0.002$).

The median follow-up lengths for the intervention and control groups were 44 days (38–54 d) and 43 days (28–62 d) ($p = 0.721$). The cumulative survival and

TABLE 1.
General Characteristics of Participants

Variables	Intervention ($n = 48$)	Control ($n = 53$)	p
Gender (male/female), *n* (%)	24 (50)/24 (50)	25 (47)/28 (53)	0.77
Alertness[a], *n* (%)	30 (62)	16 (30)	0.001
Age, yr, mean ± SD	63 ± 16	69 ± 16	0.29
Acute Physiology and Chronic Health Evaluation II score, median (interquartile range)	29 (26–32)	27 (22–31)	0.65
Use of glucocorticoid, *n* (%)	35 (73)	39 (71)	0.88
Previous use of neuromuscular blocker, *n* (%)	12 (25)	13 (24)	0.86
Previous use of sedatives, d, median (interquartile range)	9 (3–14)	7 (2–11)	0.27
Renal replacement therapy, %	87.5	81.1	0.425
Conditions precipitating ICU admission, *n* (%)			
Sepsis	25 (52.1)	26 (49.1)	0.92
Pneumonia	11 (22.9)	11 (20.8)	0.98
Chronic obstructive pulmonary disease	04 (8.3)	04 (7.5)	0.82
Stroke	03 (6.2)	05 (9.4)	0.82
Acute respiratory distress syndrome	02 (4.2)	02 (3.8)	0.68
Brain trauma	01 (2.1)	02 (3.8)	0.93
Cardiopulmonary resuscitation	02 (4.2)	03 (5.6)	0.91

[a]"Yes" if Richmond Agitation-Sedation Scale from −1 to +1.

the cumulative weaning success in the IMT group and controls are depicted in (**Fig. 2**). There was a significant difference in survival in favor of the intervention group at the 60th day (71.1% vs 48.9%; $p = 0.030$) (Fig. 2*A*). The cumulative rate of weaning success was higher in the intervention group (74.8% vs 44.5%; $p = 0.001$) (Fig. 2*B*).

In the multivariate Cox proportional hazards model, IMT was strongly associated with weaning success (HR, 2.27; 95% CI, 1.32–3.91; $p < 0.003$) (**Table 3**). Besides, duration of MV before randomization was inversely associated with weaning success (HR, 0.93; 95% CI, 0.90–0.95; $p < 0.001$).

DISCUSSION

In the present study, we evaluated the impact of an IMT program on muscle strength and the rates of weaning success and survival in tracheostomized ICU patients on prolonged weaning. A software guided electronic device was used for setting the target load.

The IMT program was associated with a significantly higher increase in the absolute values of PImax (26.1 ± 18.5 cm H_2O) and the TIE index (0.93 ± 0.73 cm H_2O/s) in comparison with no intervention (corresponding numbers of 7.5 ± 19.7 cm H_2O and 0.24 ± 0.60 cm H_2O/s, respectively, $p < 0.001$ for both comparisons). Comparisons between studies are not easy given the differences regarding the duration of the training period, the applied loads, and the strategy adopted to measure PImax. However, the magnitude of the increase in the PImax in the present study was substantially higher than the ones reported in previous studies employing mechanical loading devices, in which the gain varied from 6 to 24 cm H_2O (11, 12, 19, 20). The sole study using an electronic loading device reported a gain of 30 cm H_2O in the PImax after 2 weeks of IMT (19), a number very close to ours. The percent

TABLE 2.
Comparison Between Control and Intervention Groups as to Selected Ventilatory Variables and Respiratory Function

	Intervention ($n = 48$)	Control ($n = 53$)	p
Duration of mechanical ventilation pre randomization, d, median (interquartile range)	23 (15–32)	20 (12–28)	0.256
TIE index at start, cm H_2O/s, median (interquartile range)	0.78 (0.68–0.88)	0.87 (0.56–1.01)	0.357
TIE index at the end of follow-up or prior to either SW or DoMV, cm H_2O/s, median (interquartile range)	1.56 (1.25–2.08)	0.99 (0.65–1.71)	0.001
PImax at start, cm H_2O, median (interquartile range)	−42.5 (29.0–51.0)	−41.0 (35.0–58.0)	0.327
PImax at the end of follow-up or prior to either SW or DoMV, cm H_2O, median (interquartile range)	−75.0 (51.0–82.5)	−48.0 (36.0–72.0)	0.003
Interruptions of the weaning trials, *n* (%)			
0	4 (8.4)	3 (5.7)	0.89
1	22 (45.8)	9 (17.0)	0.004
≥ 2	22 (45.8)	41 (77.4)	0.002

DoMV = death on mechanical ventilation, PImax = maximal inspiratory pressure, SW = successful weaning, TIE = timed inspiratory effort.

increase in the TIE index (136% ± 136%) was even higher than in the PImax (106% ± 175%) in the intervention group, but the scarcity of studies using this index in this scenario prevents comparisons with the literature. The frequency of two or more interruptions along the weaning process was significantly lower in the intervention group.

The use of IMT as an adjuvant in MV weaning was the subject of a recent and comprehensive systematic review (8). Few studies addressed the use of IMT in prolonged and difficult weaning in a controlled fashion, and most of them resorted to a mechanical loading-generating device for the training (11, 12, 21).

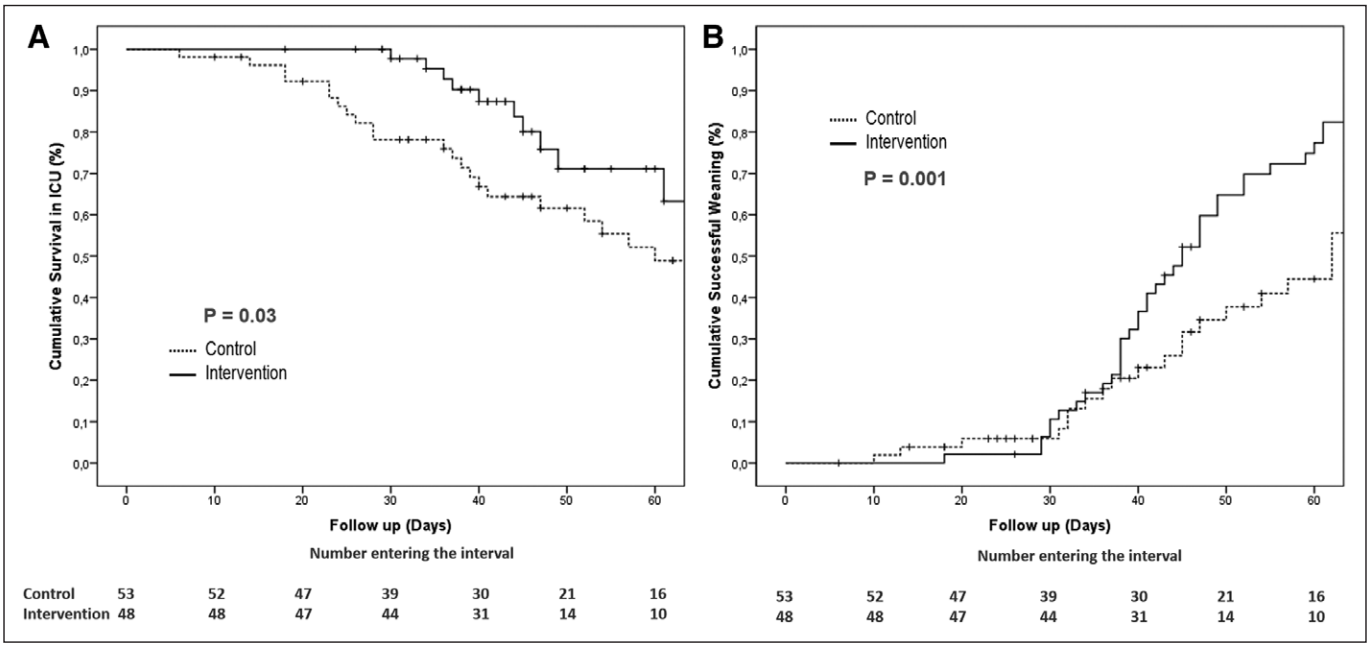

Figure 2. Kaplan-Meier curves showing the cumulative survival in (**A**) and cumulative weaning success (**B**) for the first 60 d of ICU.

TABLE 3.
Multivariate Cox Regression Analysis to Test for Association of the Inspiratory Muscle Training With the Time Until Successful Weaning Adjusted for Selected Confounding Factors

Coefficients	Hazard Ratio (95% CI)	*p*
Inspiratory muscle training	2.27 (1.32–3.91)	0.003
Age, yr	0.98 (0.97–1.00)	0.075
Gender (male)	1.40 (0.82–2.39)	0.207
Skin color (non-White)	0.99 (0.60–1.64)	0.987
Acute Physiology and Chronic Health Evaluation II score	0.98 (0.93–1.03)	0.473
Alertness (yes/no)[a]	1.52 (0.87–2.64)	0.137
Duration of mechanical ventilation before randomization, d	0.93 (0.90–0.95)	< 0.001

[a]Yes if Richmond Agitation-Sedation Scale from −1 to +1.

Interestingly, the mean weaning time in the most extensive study was 18.0 days in the control group and 14.4 days in the intervention group (12), numbers comparable with ours (24 d and 15 d, respectively). We could only find one small study that used an electronic loading-generating device for the IMT (19). The weaning time in that study was substantially shorter than in ours (9.4 d in controls and 3.5 d in the intervention group), but their patients were younger and healthier (as can be judged by their lower Acute Physiology and Chronic Health Evaluation II scores). We could not compare our results regarding the impact of the IMT on the number of interruptions of the weaning process because this variable was not subject to analysis in previous studies. In this regard, it is our view that the muscle strength gain along with the IMT program, as indicated by the increase in the TIE index values, may have prevented some interruptions thereby reducing the weaning time.

After randomization, a statistically significant difference was found regarding the frequency of alertness in favor of the intervention group. To account for the statistically significant difference observed between groups regarding alertness status, we resort to three post hoc statistical analyses using weaning success as the outcome. When testing for the success rates of the control group factored by the alertness status (yes vs no), no statistically significant difference was found (43.7% vs 32.4%; respectively, $p = 0.536$); corresponding numbers for the intervention group were 70.0% versus 72.2%, p equals to 1.000. Finally, the success rates of nonalert participants factored by the group they belong to (intervention vs control) were 72.2% versus 32.4%, p equals to 0.009. These analyses were unable to show any significant association of the alertness status with the weaning outcome and confirmed the role of IMT in improving the success rate of the MV liberation.

Interestingly, a recent update regarding IMT in critical care suggests that patients on MV should be alert and cooperative in order to be considered for the procedure (22). Our findings show that IMT can also be undertaken and offer benefits to nonalert patients on MV, but further studies are required to substantiate this subject better.

In a recent review whose primary subject was VIDD, authors emphasized the scarcity of studies examining the impact of the IMT program on the muscle strength and put an especial emphasis in the shortage of studies addressing the most critical issues in this regard: clinical outcomes (23). The main endpoints of our trial, the cumulative ICU survival rate, and the cumulative weaning success rate are outlined in Figure 2, in which a statistically significant benefit of the IMT program was found for both outcomes. Our findings regarding improvement in the weaning success rate are consistent with those from a previous study employing a mechanical loading-generating device for the training (12). As far as we could know, the impact of an IMT program on the patient's survival was not addressed before placing our results as the first in the literature reporting such clinically relevant outcomes.

To better explore the association of the IMT program with the weaning success, we developed a multivariate

Cox proportional hazard regression model in which adjustments were performed for every potentially confounding factor available. The IMT program was strongly and positively associated with weaning success. As expected, weaning success was negatively associated with the duration of MV before randomization. In addition, there was a trend for a negative association with aging, but statistical significance was not found. A more prolonged duration of MV before randomization and senescence are widely recognized predisposing factors to VIDD (23).

Our results are encouraging, but the study presents some limitations. Due to the nature of the study, blinding was not possible. Caution should be exercised especially regarding external validity and negative findings interpretation considering the single-center feature of the research and the small sample size. The definition used for successful weaning was not the recently introduced one (17), which was not available by the time the study was designed and registered. Finally, the prevalence of "alertness" was higher in the IMT group than in the control one weakening our conclusions.

Nevertheless, these limitations do not detract from the valuable information generated by the study. More extensive studies are needed to confirm our findings.

CONCLUSIONS

Our findings have shown that the use of an IMT program with an electronic resistive loading device was associated with substantial muscle strength gain. More importantly, the strategy was associated with positive impacts in two very relevant clinical outcomes: the rates of survival and successful weaning.

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This study was approved by the local Research Ethics Committee and was registered in a publicly accessible clinical trial database (ClinicalTrials.gov ID: NCT02932189). Approved by the institution's ethics committee under the number 45060215.3.0000.0065.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

All authors contributed substantially to the study design, data analysis and interpretation, and the writing of the article. All authors read and approved the final article.

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