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Comparison of the impact of three inspiratory muscle training programs on diaphragm strength and endurance in intubated and mechanically ventilated patients with difficult weaning : a multicentric randomized controlled trial

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Abstract

Background: Inspiratory muscle training (IMT) consists of a resistive inspiratory maneuver through a pressure device comprising a unidirectional valve that hinders inspiration. IMT was found to significantly increase inspiratory muscle strength in adults undergoing invasive Mechanical ventilation (MV). Despite, it exists an important heterogeneity of IMT protocols, and it is unclear if it reduces MV duration. Furthermore, inspiratory muscles endurance is scantly evaluated while the assessment of this function may be fundamental for a successful weaning. In this multicentric controlled randomized parallel trial, we compared the effects of three different IMT protocols (low, high and mixed intensity) on inspiratory muscle strength and endurance in difficult to wean patients in two intensive care units (ICU).

Methods: 92 subjects presenting difficult weaning were randomized in 3 groups to perform one IMT protocol twice daily. The primary outcome was the Maximal Inspiratory Pressure (MIP) increase in each group after successful extubation or 30-days. Secondary outcomes were Pressure peak increase (Ppk), as endurance marker, weaning duration, and safety.

Results: During the weaning process, the observed increase of MIP was 12.2 ±11.2 cmH_2O in the mixed intensity group (EDRIC), 5.3 ±15.5 cmH_2O in the low intensity group (CADER), and 6.8 ±15.1 cmH_2O in the high intensity group (MARTIN). There was a non-statistically significant difference between EDRIC group and CADER group (mean adjusted difference: -6.65, 97.5%CI [-14.35; 1.04], p=0.052), neither between EDRIC group nor MARTIN group (mean adjusted difference: -3.67, 97.5%CI [-11.52; 4.18], p=0.289).

No significant difference in Ppk increase were observed between the three groups. Over 358 IMT sessions, only 3 serious adverse events (spontaneously reversible bradycardia) were considered possibly related to the study.

Conclusion: Independently of IMT protocol applied, MIP and Ppk seemed to improve in our cohort of difficult to wean patients. Ppk could be a helpful tool to assess diaphragm function exhaustively. EDRIC group showed a slightly higher efficacity.

INTRODUCTION

Patients under prolonged invasive mechanical ventilation (MV) in intensive care unit (ICU) represent 40–70% of total patients hospitalized in ICU [1]. This situation will generate very significant costs, those inherent to the increased burden of infectious complications [2] and in the increased length of the stay in ICU [3]. Furthermore, there is an increment of mortality associated with the increased duration of MV [4].

Weaning from MV is the whole process allowing the progressive passage from a respiratory assistance to spontaneous breathing. This process represents 40 to 50% of the total duration of the MV, and up to 20% patients are classified in difficult to wean category after the first single breathing trial failure or extubation failure [5]. These patients presenting difficult or prolonged weaning cause similarly disproportionate health costs [6], with a significant increased burden in ICU and hospital length of stay, morbidity and

mortality [7–8]. Furthermore, these patients may develop during MV period a Ventilator induced diaphragmatic dysfunction (VIDD). VIDD consists on the inability of the diaphragm to generate sufficient force over time to provide an effective ventilation, causing a delayed weaning from mechanical ventilation [9]. It seems to appear just after 18 hours of controlled MV [10] and is characterized by a deficit in strength and endurance without neurological impairment. Thus, inspiratory muscles training (IMT) in intubated and mechanically ventilated patients in ICU is a non-pharmacological therapeutic option to be explored to fight against VIDD and consequently, to decrease duration of MV on these population of patients. It exists different programs to apply IMT and it seems feasible without any deleterious side effects. However, a recent meta-analysis [11] concluded that new studies are necessary to measure the impact of IMT on the duration of ventilatory withdrawal, as there is scant evidence and no study demonstrating any benefit of IMT over the duration of weaning.. The main culprit of IMT is the heterogeneity of programs applied. proposing indistinctively endurance gain programs (many repetitions and low resistance) [12], and pure strength gain programs (few repetitions and highest resistance tolerated) [13]. Thus, we can expect to observe different improvement depending on the protocol applied. Besides, there is no evidence testing a mixed inspiratory muscle strengthening program.

Consequently, we have designed this clinical study assessing three different IMT programs, strength, endurance and a mixed program in ICU difficult to wean patients to evaluate force, endurance and safety in ICU difficult to wean patients.

METHODS

Study design:

We conducted a multicenter prospective, superiority randomized, single-blind clinical trial in two medical ICU at Bordeaux University Hospital and Lyon University Hospital (France) with three parallel groups and an unbalanced randomization ratio in favor of the EDRIC group (2:1:1) (Fig. 1) according to a computer-generated randomization list with stratification on the study center and permuted blocks of varying size (4 and 8).

Randomisation was performed by the physiotherapist after confirmation of participant's eligibility using a web-based centralized system. Participants and physiotherapists were not blinded to treatment allocation but the physicians responsible for the extubation decision were blinded to the IMT protocol received..

The study was approved by an independant ethics committee (comité de protections des personnes sud-ouest et outre mer III; DC 2016/03; NCT02855619). The present study report adheres to the CONSORT statement and is compliant with Helsinki declaration.

Population:

Adult patients (> 18y.o.) who spent > 18 hours in a controlled mechanical ventilation mode, with weaning criteria's defined by the European consensus conference in 2007 defined as sedation decreased,

spontaneous breathing cycles, $PaO_2/FIO_2 \geq 150$, absence of inotropes or vasopressors at high doses or increasing doses (< 1mg/h), oxyhemoglobin saturation (SaO_2) > 90% with $FiO_2 \leq 50\%$, PEEP ≤ 8cmH_2O, temperature between 36°C and 39°C, Glasgow score ≥ 8) [5], and who failed the first spontaneous breathing trial (SBT) were evaluated for inclusion. Similarly, we excluded patients with hemodynamic and respiratory instability, severe ventricular arrhythmias, poor short-term vital prognosis, cardiac arrest with a guarded neurological prognosis, proven neuro-degenerative pathology, tracheotomy, current pregnancy, do-not-resuscitate order.

Interventions:

Patients were included in the 48h after the first failed SBT or failed extubation if they have the eligibility criteria afore mentioned and after the next of kin provided consent, and they were randomized in one of the three groups of IMT protocols (Fig. 2).

All subjects received IMT interventions twice daily with at least 4 hours between interventions, 7 days per week, from inclusion to successful extubation or 30 days (D30), whichever occurred first. As consciousness or general stability may evolved unfavorably or was fluctuating, the inclusion criteria were checked daily and mandatory to allow patients perform IMT sessions. Before each training session, patients were positioned in 45-deg Fowler's position and cardiorespiratory variables were assessed to ensure that they did not perform training if they were hemodynamically unstable, defined as: respiratory rate (RR) > 35 bpm, SaO_2 < 90%, systolic blood pressures (SBP) > 180 mmHg or < 90 mmHg, paradoxical breathing, agitation, and/or tachycardia. The maximal inspiratory pressure (MIP; cmH_2O) measurement was performed daily before the first session of IMT. All patients were disconnected from MV and performed the IMT with the Threshold IMT device (Philips Respironics;, Murrysville, PE) connected directly to the endotracheal tube. If necessary, supplementary oxygen was added.

Training sessions were interrupted in the presence of hemodynamic instability, as defined previously, and patient was reventilated in pressure-support ventilation with his previous settings.

Martin IMT protocol (high intensity): the physiotherapist applied the highest inspiratory resistance tolerated by the patient and then performs 4 sets of 6 to 10 breaths. Each series were respectively interspersed with a pause of 2 minutes where patients were similarly reconnected to MV. Titration of the highest resistance tolerated was performed as follows: firstly, setting during the first session was made against 9 cmH_20 (the lowest load possible of the threshold IMT device) and then + 0 or + 2 or + 5cmH_2O increases at each set depending on patient tolerance and physiotherapist evaluation. Each day the sessions were initiated with the highest resistance from previous day, and increased resistance of + 0, +2 or + 5cmH2O at each set, similarly (12).

Cader IMT protocol (low intensity)

the physiotherapist applied a single inspiratory resistance of 30% of the MIP measured on the day of inclusion. The patient then inhaled against resistance for 5 minutes. Once the session was fully

completed, the load was increased by 10% of the initial MIP until 100% (13)

EDRIC IMT protocol (mixed intensity)

in this novel protocol the physiotherapist set the inspiratory resistance device to 30% of the previously measured MIP. Then, the patient faced with inspiratory resistance during 20 breaths. With each set, resistance was increased by 10% of the MIP of the day until reaching a resistance equivalent to 60% of the MIP in the 4th set. Each series were respectively interspersed with a pause to reconnect patients to MV for 2 minutes.

Measurements:

The primary outcome was the evolution of strength between randomisation day (D1) and successful extubation or D30 using MIP as surrogated measurement and (cmH_2O) performed following the recommendations of the American Thoracic Society [14]. We used a unidirectional expiratory valve attached to the endotracheal tube (ETT) and to an external pneumotachograph (Fluxmed GrH monitor; MBMED, Buenos Aires, AR). Each measure was performed three times for 20 seconds each, and the best of the three measurements was conserved to final analysis.

The main secondary outcome was the evolution of endurance using a test, validated in COPD patients [15], against an external load with an increased threshold to assess pressure peak (Ppk; cmH_2O). Ppk consists in breathing through an external resistance device, as used in inspiratory muscle strengthening programs, with a resistance starting at 30% of the initial MIP and increasing by 10% every 2 minutes until the effort is no longer tolerated by the patient. The maximum pressure tolerated for 2 minutes by the patient is the Ppk.

To ensure a comparison of this endurance indicator between patients, we evaluate Ppk stages evolutions, from stage 0 (2 minutes untolerated breathing against threshold at 30% initial MIP) to stage 8 (2 minutes breathing against threshold at 100% of initial MIP), with an increasing of the threshold by 10% each 2 minutes from 30–100% of initial MIP.

Patient's tolerance limit was determined when they reached one of the following thresholds: HR>(220-age)/min, SaO_2 < 88%, SBP > 180mmHg or < 90mmHg, or RR > 35/min, patient willing to discontinue intervention.

The other secondary outcomes were weaning duration defined by the number of days between inclusion and successful extubation (> 48h without reintubation), ICU length of stay (days), reintubation rate and safety assessed with the occurrence of adverse events. All adverse events were collected by a clinical research associate and analyzed by the sponsor’s clinical trial vigilance unit to assess the eventual relation with the study.

Statistical analysis:

A statistical analysis plan was developed and validated by the trial steering committee before the final database lock and analyses.

The expected MIP increase was − 12cmH_2O in EDRIC group, and − 9.7cmH_2O in Martin group and − 9.9 cmH_2O in Cader group, as reported by the authors (Martin et al, 2011; Cader et al, 2010) (12,13), with a common standard deviation of 2.5 cmH2O. It was considered that an increase of 2 cmH_2O in the EDRIC group is a minimum threshold of additional gain compared to the two other groups to allow a clinical benefit for the patients (corresponds to a 20% increase in the inspiratory force measurement). The study was therefore constructed in such a way as to highlight a difference equal to or greater than this threshold.

As the EDRIC group was compared to each of the two other groups for the primary objective, the two-sided type 1 error rate was set at 0.025 using a Bonferroni correction. With an 80% power, 88 participants were required in total (44 for EDRIC, 22 for Martin and 22 for Cader).

Qualitative variables were described in terms of numbers and percentages and quantitative variables in terms of total number, mean, standard deviation, median, minimum, maximum, 1st and 3rd quartile, overall and by procedure group. The primary analysis was conducted on an intent-to-treat basis using the strategy for replacing missing data of the “last observation carried forward” (LOCF) type (i.e. when a MIP value was missing at day 30 or on the successful extubation day, the change in MIP between baseline and the last available follow-up value was used). In the special case where a participant had a failed extubation on day 30 and an end-of-study MIP measurement on the same day, we used the MIP value before extubation. The primary outcome was compared using a linear regression model adjusted for study center, for the MIP measurement on D1 centered on the median and the presence of a respiratory pathology at inclusion, identified as a prognostic factor for extubation failure.. A post-hoc subgroup analysis in participants with severe VIDD (baseline MIP < 36cmH_2O, [16]) was then performed.

The same analytical strategy was conducted for the comparison of Ppk stage between D1 and successful extubation or D30 (end of follow-up). A post-hoc analysis was conducted to compare between groups the proportion of participants with an increase of at least one Ppk stage between D1 and successful extubation or D30 (end of follow-up), using a logistic regression model and the same covariates. One participant with a missing baseline value of Ppk was not included in those analyses. Analysis of the other secondary outcomes was conducted on complete cases.

The main analysis was performed at a two-sided overall type 1 error rate of 5%, with a p-value threshold of 2.5% for each of the two comparisons (EDRIC vs Cader, EDRIC vs Martin). For a given comparison (EDRIC vs Cader, EDRIC vs Martin), if, and only if, the null hypothesis for the primary endpoint (MIP) was rejected, then a statistical comparison on the secondary endpoint Ppk was performed at the same two-sided alpha threshold of 2.5%. If the null hypothesis for the primary outcome was not rejected, there was no hypothesis testing on Ppk for that comparison. No hypothesis testing was conducted for the other secondary objectives. All statistical analyses were performed with SAS v.9.4 software (SAS Institute).

RESULTS

Flow participants

A total of 177 patients were screened from October 2016 to January 2020, and 92 randomized (Fig. 3).

Baseline characteristics of the study population are presented in Table 1.

Table 1
Baseline characteristics of participants

		Groupe EDRIC	Groupe Martin	Groupe Cader
Anthropometric data				
Patients (number)	N	43	23	23
Age (years)	Mean (SD)	65.2 (10.6)	67.6 (11.3)	66.4 (9.8)
Gender (number/ %)	Malen%	27 62.8%	15 65.2%	15 65.2%
	Female %	16 37.2%	8 34.8%	8 34.8%
Pre-existing medical/surgical pathology	N %	35 81.4%	18 78.3%	18 78.3%
Cause of MV introduction				
ARDS	N %	12 27.9%	6 26.1%	12 52.2%
postoperative	N %	5 11.6%	3 13.0%	1 4.3%
Cardiac failure	N %	5 11.7%	5 21.7%	6 26.1%
Pneumonia	N %	14 32.6%	14 60.9%	10 43.5%
Sepsis	N %	13 30.2%	10 43.5%	7 30.4%
Coma	N %	12 27.9%	3 13.0%	5 21.7%
Associated treatments				
Curare	N %	21 48.8%	11 47.8%	9 39.1%
Endotracheal tube size (mm)	Mean (SD)	7.5 (0.35)	7.5 (0.4)	7.5 (0.14)
Other data				
SAPS II score at admission	Mean (SD)	65.0 (19.8)	65.3 (15.1)	61.4 (17.8)
GLS at inclusion	Mean (SD)	10.7 (0.8)	10.9 (0.3)	10.8 (0.4)
Length of MV before 1rst SBT(days)	Mean (SD)	6.4 (7.4)	9.9 (11.8)	8.0 (5.8)
Last PaO2/FiO2 before inclusion	Mean (SD)	247.2 (74.9)	236.7 (69.1)	236.1 (64.4)

SD = standard deviation, ARDS = Acute Respiratory Distress Syndrome, SAPS II = Simplified Acute Physiology Score, GLS = Glasgow Coma scale, MV = Mechanical Ventilation, SBT = Single Breathe Trial

Briefly, patients included had a mean age of 66 years, and they were predominantly male (57.6%). They had a mean admission Simplified Acute Physiology Score (SAPS2) of 64.1, a mean PaO_2/FIO_2 at inclusion of 241.6 and a mean time spent under MV at inclusion of 7.7 days.

Three participants were excluded due to violation of a major eligibility criteria. One patient presented a degenerative pathology, one did not respect the inclusion criteria of blood gases based on an erroneous result and the last was considered wrongly included due to a hemodynamic instability detected just after inclusion; 89 participants were included to the final analyses. 68 participants have been followed-up during all the weaning period and completed the study.

Strenght evaluation

The mean MIP at day 1 in the total population was 51.3 ± 17.2cmH_2O and 22 patients (24.7%) had a severe VIDD characterized by a MIP < 36 cmH_2O at day 1.

During the weaning process, observed MIP increase was 12.2 ± 11.2 cmH_2O in EDRIC group, 5.3 ± 15.5 cmH_2O in CADER group, and 6.8 ± 15.1 cmH_2O in MARTIN group. There was a non-statistically significant difference between EDRIC group and CADER group (mean adjusted difference: -6.65, 97.5%CI [-14.35; 1.04], p = 0.052), and no differences were observed between EDRIC group and MARTIN group (mean adjusted difference: -3.67, 97.5%CI [-11.52; 4.18], p = 0.289).

In this sub-group with severe VIDD, the mean MIP increase was 10.8 ± 9.3 cmH_2O in EDRIC group (n = 9), 8.4 ± 10.6cmH_2O in CADER group (n = 7), and 7.2 ± 9.8 cmH_2O in MARTIN group (n = 6). Similarly, there was also a non-statistically difference of MIP increases between EDRIC group and CADER group (mean adjusted difference: -3.12, 97.5%CI [-17.11; 10.87]), and differences between EDRIC group and MARTIN group were consistently not significants (mean adjusted difference: 1.06, 97.5%CI [-19.56; 21.69]).

Endurance evaluation

The mean Ppk stage at day1 was 1.1 as they completed stage 1 (2 minutes breathing against 30% initial PIM) but failed the second stage (< 2 minutes breathing against 40% initial PIM).

During the weaning process, the observed mean Ppk stage increased was 1.2 ± 1 in EDRIC group, 1.1 ± 1 (n = 43) in CADER group (n = 22), and 0.8 ± 1 in MARTIN group (n = 23). The mean adjusted difference between EDRIC group and Martin group was − 0.42, 97.5%CI [-1.19; 0.35] and − 0.008, 97.5%CI [-0.85; 0.69] between EDRIC group and CADER group. In consequence, 67.4% patients have increased at least one stage in EDRIC group, 47.8% patients in MARTIN group, and 54.5% patients in CADER group (OR 1,49, 97.5%CI [0,4; 5,55] in favor of EDRIC vs. CADER, and OR 2,38, 97.5%CI [0,65; 9,09] in favor of EDRIC vs MARTIN).

In the sub-group analysis with severe VIDD, the observed mean Ppk stage increased was 1.9 ± 2 in EDRIC group (n = 9), 1.4 ± 1 in CADER group (n = 7), and 1 ± 1 in MARTIN group (n = 6).

Weaning duration and reintubation rate

The mean weaning duration was 6.7 ± 5.8 days in EDRIC group (n = 36), 5.8 ± 5.1 days in MARTIN group (n = 20) and 5.5 ± 4.7 days in CADER group (n = 19°.

The reintubation rate was 7.9% in EDRIC group (n = 38), 10% in Martin group (n = 20) and 15% in CADER group (n = 20).

Safety

We recorded a total of 358 IMT sessions, with a mean duration of 14.5 ± 5.2 minutes. 6 adverse events possibly related to the study were recorded. In EDRIC group, 1 patient have presented a polypnea prior the IMT session, and in CADER group, 5 patients have presented adverse events (3 serious adverse events of bradycardia, 1 non-serious arterial hypertension and 1 non-serious isolated bradycardia).

DISCUSSION

Our findings point that during the weaning process of difficult-to-wean patients, IMT increased strength and endurance, independently of the type of intervention. Despite EDRIC group seems to be more efficient on both MIP and Ppk increase, we did not find any statistically difference between the groups.

MIP is classically the main outcome assessed in clinical trials evaluating IMT impact in invasively mechanically ventilated patients. Cader et al. [12] showed in 41 patients who were ventilated for at least 48 hours, comparing IMT to a control group with exclusively usual care. They observed a mean difference increase of MIP of 7.6 cmH_2O (95% CI 5.8; 9.4) during the weaning period. Interestingly, Cader et al. included elderly intubated patients (> 70 years old) with very low MIP values (< 20 cmH_2O) at the initiation of the weaning process, which may suggest a higher response in patients initiating IMT with lower MIP baseline values. Conversely, Martin et al. [13] performed a clinical study in 69 tracheostomized difficult to wean patients comparing IMT to a sham intervention. The IMT group show a pre-post training MIP significant increase (-44.4 ± 18.4 vs. -54.1 ± 17.8 cmH2O, p < 0.0001), while the SHAM group MIP change was not significant (-43.5 ± 17.8 vs. -45.1 ± 19.5 cmH2O, p = 0.39). Of note, patients included spent a mean time of 41.9 days on MV, which may explain their results. These results seem to not be corroborated in our study. These could be explained by a very heterogeneous MIP at inclusion with higher mean values at inclusion (49.7 ± 17.4 cmH_2O) than the populations previously described by Cader and Martin. Furthermore, only 24.7% of our included patients presented a severe VIDD, characterized by a MIP < 36 cmH_2O [16]. If we focus int this subgroup of patients, mean MIP and Ppk stage increase during weaning with a better result in EDRIC group. This suggest that patients with lower MIP are more respondents to IMT to increase their diaphragmatic strength and endurance. Similarly, it suggests the importance to assess VIDD but adding a Ppk measure, allowing a more complete evaluation of the diaphragm.

Trivedi S et al. showed in a cohort of 1283 of patients who failed their first extubation attempt and underwent a second extubation that MIP was consistently higher in patients with a re-extubation success than those presenting a re-extubation failure (41 ± 12 cmH2O vs. 38 ± 13 cmH2O), p = 0.02) [17]. Our

patients had higher mean MIP values which does not correspond completely with the population previously described. This could lead to a better success of outcomes and a lower improvement of MIP.

We considered that IMT protocols presented in Cader and Martin studies were effectives and well tolerated; although, we considered these two protocols as control groups as we presumed that diaphragmatic performances could be highly improved with our novel IMT. In our replication of Cader IMT protocol, we observed a MIP increase of 4.5 vs 7.6 cmH_2O compared to Cader's original study [12]. Similarly, in our reproduction of Martin protocol, found a MIP increase of 6.7 vs 9.7 cmH_2O in Martin's original study [13]. An important element which explains these results is that populations are totally different. Cader et al. (12) included elderly intubated patients (> 70 years) with very low MIP (< 20 cmH_2O) at the initiation of the weaning process, suggesting MIP increase is larger in patients with low initial MIP. Finally, Martin et al. (13) included difficult to wean tracheostomized patients after a mean of 41.9 days over MV patients.

Time to start IMT is crucial and it is still under debate. A recent systematic review and meta-analysis showed that IMT in ICU is started during early MV in 8 studies, after proved difficult to wean and frequently in tracheostomized patients in 14 studies, and after extubation in 3 studies [18]. Bisset et al have elaborated a practical guide to perform IMT in ICU which give an interesting base for clinicians (19). They encourage clinicians to consider IMT after 7 days of MV. In our study, we choose to initiate diaphragmatic rehabilitation just after the first SBT failure to select patients who need help for weaning of MV, that correspond at a mean of 7.7 days of MV, close to Bisset et al. recommendations. We consciously believe that every therapeutics which could contribute to accelerate the weaning process should be initiated as soon as possible if necessary, especially with safety and feasible therapeutics like IMT.

Some limitation merits to be considered. Firstly, we considered in our study that IMT protocols presented by Cader et al. and Martin et al. were effective and well tolerated. Otherwise, we estimated that our mixt program may highly improve diaphragmatic performance; in consequence, we considered both two IMT protocols as control groups However, it would be interesting to compare these different interventions to standard of care without any IMT intervention. Indeed, we can expect that a RCT without a true control group may lead to a lack of signification between groups as we could assume that all the interventions were equally efficacity. Similarly, the absence of blindness can't exclude totally a measurement bias. Similarly, a main limitation is the hitch to clearly select difficult to wean patients which should have been more targeted to ensure that patients included had a diaphragmatic impairment. Unfortunately, to determine the principal cause of SBT failure is complicated as this is a multifactorial process with different clinical conditions interacting. Finally, the heterogeneity observed in MIP evolution was higher than anticipated at study design, which has led to a likely underpowered study with non-statistically significant results, even if the point estimates of the MIP differences in favor of EDRIC were above the predefined clinically meaningful threshold of 2cmH2O.

Quality of life seems to be a parameter usually neglected in clinical trials in these population of patients. We only find a study performed by Bisset et al. evaluating 70 patients mechanically ventilated > 7 days, successfully extubated for 48 hours, and performing a 2 weeks IMT intervention compared to a usual care group [19]. In this study, they observed a significant increase between groups in EQ5D (14 points IMT group vs 2 points usual care group; p = 0.034). Unfortunately, there was no statistically significant difference in SF-36, but we can estimate a potential benefit as the mean difference was 0.05 (95% CI = −0.01 to 0.10). In consequence, future studies should explore if IMT has any benefits in short term and long-term quality of life as primary outcome. Similarly, we should assess the effects of this intervention on hospital or ICU readmission rates to evaluate any impact on outcomes beyond the hospital stay.

CONCLUSION

In difficult to wean patients receiving invasive MV, three different IMT programs seems to be equally efficacy to improve strength and endurance. EDRIC group (mixed intensity) trend to increase strength and endurance compared to Cader (low intensity) and Martin (high intensity) programs but without significant differences. IMT seems to be safe, and few serious transient adverse events were observed, majority of them in Cader training group. Ppk could be a helpful option to perform a better VIDD assessment. These findings call for future clinical trials being focused on patients with a diagnosis of VIDD and to evaluate IMT on major clinical outcomes in intubated and critically ill patients.

Declarations

Ethics approval and consent to participate: This study was performed in accordance with the declaration of Helsinki and was approved by the correspondent ethics committee (*comité de protections des personnes sud-ouest et outre mer III*; DC 2016/03).

Consent for publication: Not applicable

Availability of data and materials: Thomas Réginault and Frédéric Vargas had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Competing interests: No conflict of interest related to the article exist for any of the authors involved in this study.

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Authors' contributions: *Study concept and design:* TR, FV; *Acquisition of data:* TR, JFB; *Analysis and interpretation of data:* TR, FV, RMA, EF, RC; *Statistical analysis:* RC; *Drafting of the manuscript:* TR; *Critical revision of the manuscript for important intellectual content:* FV, RMA, EF, JFB.

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Figures

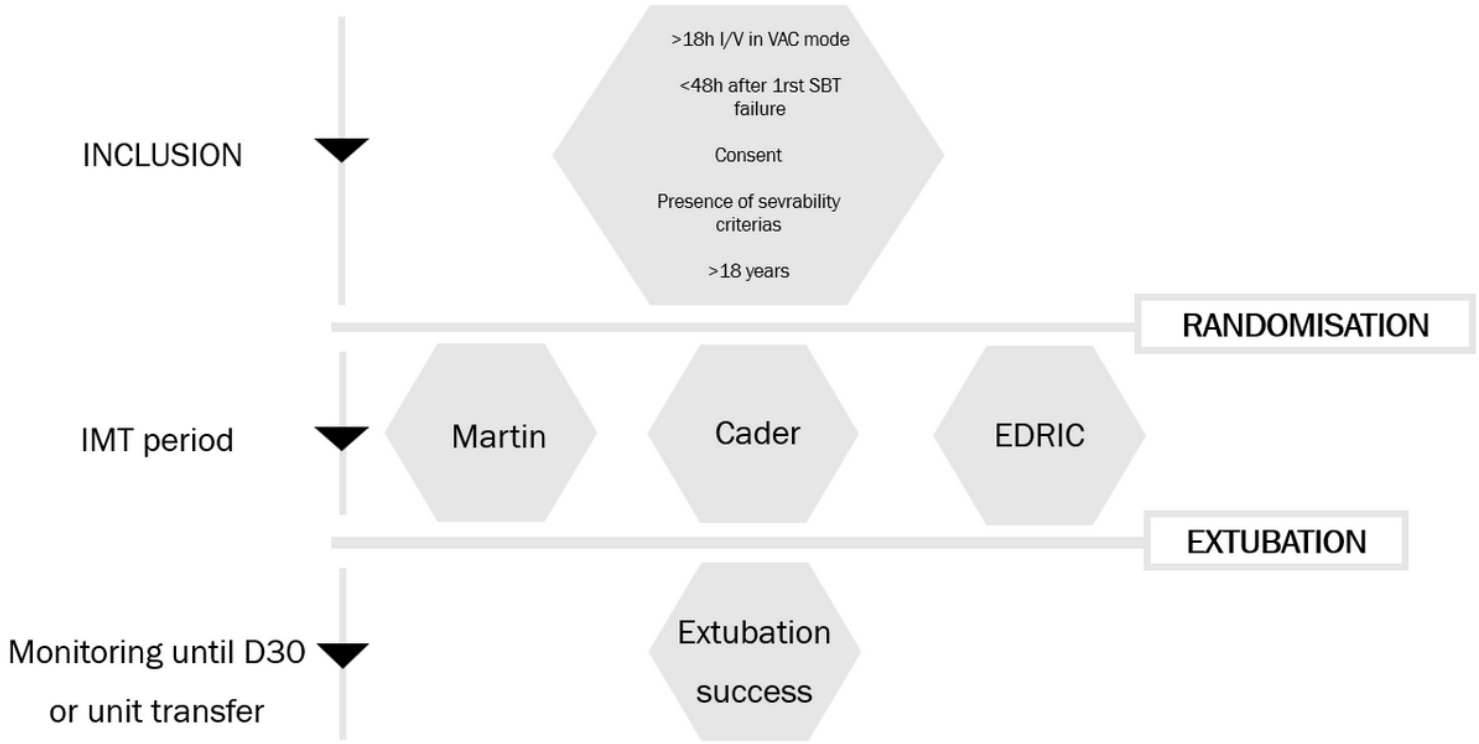

Figure 1

Study design

Programs	MARTIN	CADER	EDRIC
Description	4 sets x 6 breaths against maximal load tolerated Twice daily, 7days/week	5' against a load of 30% initial MIP with an increasement of 10%/day when the session is fully completed Twice daily, 7days/week	4 sets x 20 breaths against an increasing load at each set from 30% to 60% of daily's MIP Twice daily, 7days/week

Figure 2

Description of the 3 IMT programs

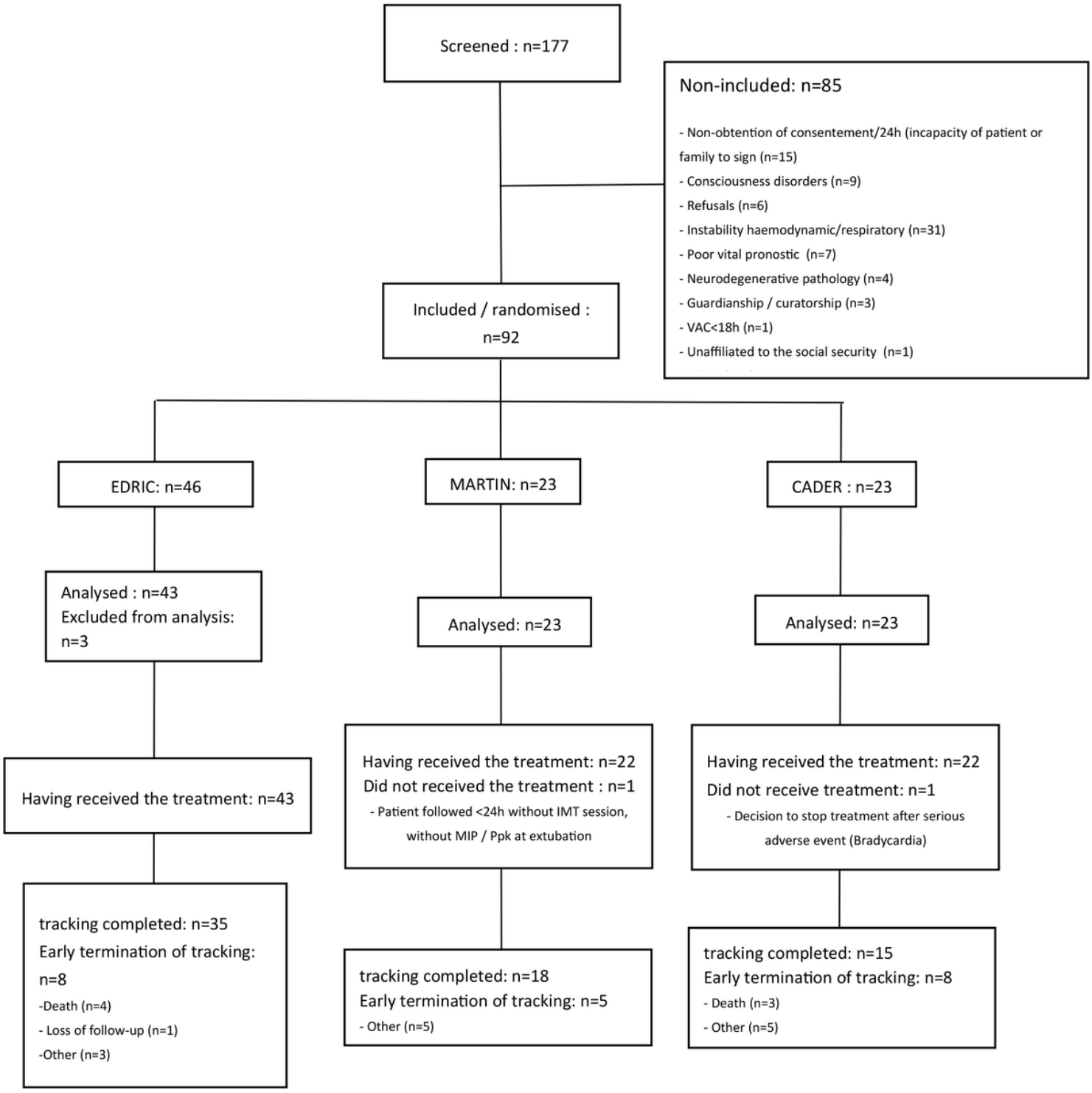

Figure 3

Flow chart of the study