Inspiratory muscle training in mechanical ventilation: suitable protocols and endpoints, the key to clear results - a critical review

Treinamento muscular inspiratório em ventilação mecânica: protocolos e parâmetros adequados, a chave para resultados claros- uma revisão crítica

SILVA, Paulo Eugênio[1]

Abstract

Definitely, mechanical ventilation (MV) is a life-saving treatment in the intensive care unit (ICU), but it is also a double-edged sword. Forty percent of the overall time spent in the ICU was reported to be devoted to weaning of MV. The major cause of weaning failure is the imbalance between the imposed load on the respiratory system and its capacity to overcome that. Thus, since the 1980's numerous studies with inspiratory muscle training (IMT) have been conducted in an attempt to reduce weaning and MV time in prolonged mechanically ventilated patients. Despite dozens of published research, only 5 randomized controlled trials (RCT) were conducted until this date. Nevertheless, it was not yet clear whether IMT led to a shorter duration of mechanical ventilation, improved weaning success, or improved survival. These RCT show considerable heterogeneity among them and possible bias that could have impaired their results. Thus, some questions may be made to highlight main points: What is the ideal prescription of IMT for patients on MV? What is the best time to measure treatment effect? Which kind of device should be used to IMT? What are the best endpoints to evaluate the effects of IMT on the process of discontinuing from MV? IMT on mechanically ventilated patients seems to be a promissory treatment despite controversial results. Therefore, RCTs should be carried out to verify the efficacy of new protocols in different approaches.

Keywords: Breathing exercises; Extubation; Inspiratory muscle training; Physiotherapy; Ventilator dependence; Ventilator weaning.

[1] Faculdade de Educação Física, Universidade de Brasília. Email: pauloeugenio@ymail.com

Introduction

Definitely mechanical ventilation (MV) is a life-saving treatment in the intensive care unit (ICU), but it is also a double-edged sword. Every year, 27 billion U.S. dollars are spent on patients requiring mechanical ventilation[1]. The increase in the rate of patients who remain in prolonged MV is higher than the annual rate of hospitalization, 5.1% versus 1.2% respectively[2]. Twenty percent of the patients experience difficulty weaning due to a combination of the unresolved primary illness or a pre-existing cardiorespiratory or neuromuscular disease. Forty-one percent of the overall time spent in the ICU was reported to be devoted to weaning with large differences between patients with various etiologies necessitating mechanical ventilation[3].

Weaning failure is strongly linked to respiratory muscle weakness. Even before the publication of Vassilakopoulos et al.[4], that defined the decreasing strength of the diaphragm caused by MV as ventilator-induced diaphragmatic dysfunction (VIDD), numerous efforts have been made to reduce the incidence of this disease[5]. The presence of VIDD is associated with increased duration of mechanical ventilation and the prevention or treatment of it is critical[5-7].

Many strategies have been done to decrease weaning time and consequently the time spent on mechanical ventilation. The inspiratory muscles training (IMT) is one of the options on arsenal. Thus, since the 80's numerous studies with IMT have been conducted in an attempt to reduce weaning and MV time in prolonged mechanically ventilated patients[5-7]. However, so far, the use of IMT in mechanically ventilated patients has limited evidences with discordant results in publications[8]. This review aimed to address the most important RCTs about IMT on mechanically ventilated patients and their potential sources of bias.

Determinants of Weaning Failure

The major cause of weaning failure is the imbalance between the imposed load on the respiratory system and its capacity to overcome that[9,10]. An important marker to comprehend this is TTdi. Until recently it was believed that the maintenance of patients in assisted mode of ventilation as pressure support ventilation (PSV) was enough to prevent decreasing on MIP. However, it has been shown that this depends on the degree of support established, since elevated levels of PSV can draw up to 96% of the diaphragm work[11]. A study on experimental animals, demonstrated that to prevent VIDD it is necessary to promote spontaneous breathing without the support of the ventilator[12]. Nevertheless, it is not clear if once VIDD is installed, only spontaneous breathing could treat this disease and if it is the most efficient treatment.

Weaning failure is strongly related to the level of diaphragm endurance[9] and this has been well demonstrated in two prospective studies that has shown the tension-time index of the diaphragm (TTdi) as an important predictor of weaning success[13,14].

The TTdi is inversely proportional to the maximum strength level of the diaphragm (figure 1). Early research with humans demonstrated that the diaphragm is fatigued when it reaches a work ratio of 40% of the maximal transdiaphragmatic pressure[15]. In healthy individuals, the TTdi average, during relaxed breathing, is 0.02, while critical values of fatigue are between 0.15 and 0.20[15,16]. Thus, MIP could be one of the determinants of weaning success, but it can not be analyzed isolated from the imposed load of the respiratory system.

Figura 1 | Fluxograma do estudo.

$$TTdi = Pdi / Pdi_{max} \times T_I / T_{tot}$$

TTdi: tension-time index of the diaphragm;
Pdi: mean transdiaphragmatic pressure swing developed with each inspiration;
Pdi_{max}: maximal transdiaphragmatic pressure;
T_I: inspiratory time;
T_{tot}: total breathing cycle duration.

Carlucci et al.[14], in a prospective observational study, found out that the average of TTdi in weaning failed patients was close to critical values and in successfully weaned patients it was normal. Latter, this research group carried out a similar study and found out the same results[13]. It is well known that IMT increases MIP in mechanically ventilated patients. Therefore, because IMT can decreases TTdi, it could impact positively on the weaning from mechanical ventilation[17,18].

Evidences of Imt on Mechanically Ventilated Patients

Despite dozens of published research, only 5 randomized controlled trial (RCT) were conducted until this date[17-21]. Caruso et al.[19], analyzed the impact of IMT on maximal inspiratory pressure (MIP), weaning time and re-intubation rate. No benefits were found in the trained group of patients. However, it is necessary to point out the kind of training used in this study. The IMT was performed using the trigger of the ventilator. It is known that adjusting the sensitivity of the ventilator is ineffective for performance gain of inspiratory muscles and other authors had previously warned of this fact[7]. Therefore, the first RCT properly conducted was only published in 2010. In this study, Cader et al.[17] with an audacious and innovative IMT protocol in mechanically ventilated patients, demonstrated that this treatment was able to reduce the weaning time and increase the MIP with statistical proof. One year later, Martin et al.[18] carried out a study using a strength IMT protocol in prolonged mechanically ventilated patients. The results corroborate with the findings from Cader et al.[17].

A systematic review of IMT in mechanically ventilated adult patients was conducted by Moodie et al.[8] and they analyzed these three cited RCTs[17-19]. IMT was found to significantly increase inspiratory muscle strength in adults undergoing mechanical ventilation. However, despite data from a substantial pooled cohort, it was not yet clear whether the increase in inspiratory muscle strength led to a shorter duration of mechanical ventilation, improved weaning success, or improved survival. These trials used in the systematic review had considerable heterogeneity on their protocols and population and these could have impaired the results. Caruso et al.[19], did the IMT with an ineffective protocol, Cader et al.[17] evaluated elderly patients precociously (in difficult weaning) with endurance IMT protocol. Martin et al.[18] carried out strength IMT in prolonged weaning patients (average of 45 days of MV). Added to these facts they used different endpoints which reduced the chances to compare them in this systematic review.

In 2012, Cader et al.[20] published another interesting RCT. The authors found that the IMT increases MIP and decreases rapid shallow breathe index (RSBI), but has no impact on “successful weaning rate" in elderly patients. In sequence Condessa et al.[21] published a RCT to evaluate the impact of IMT on weaning time, respiratory muscle strength and rapid shallow breathe index. They concluded that IMT had impact only on respiratory muscle strength.

Taking into account the latest publications related to IMT in all settings[18,22-26], MIP evaluation in mechanically ventilated patients(27), (28), as well as the whole process of discontinuing MV[29-31], some questions may arise:

-What is the ideal prescription of IMT for patients on MV?

-What is the best time to measure treatment effect?

-Which kind of device should be used to IMT?

-What are the best endpoints to evaluate the effects of IMT on the process of discontinuing from MV?

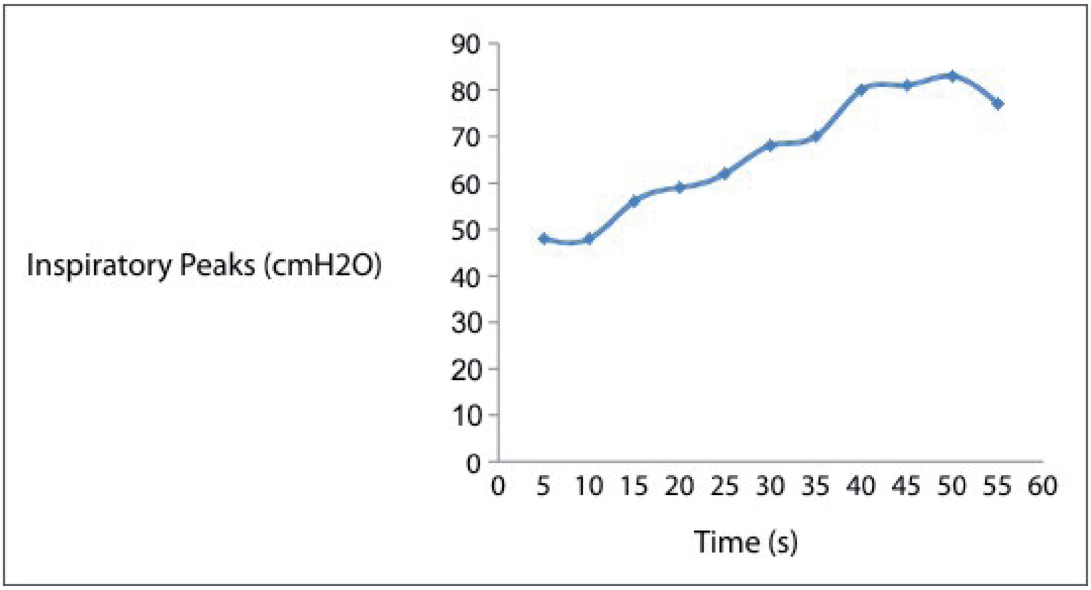
What is the Ideal Prescription of Imt for Patients on MV?

When considering the effectiveness of any type of physical training, some variables must be taken into consideration: intensity, frequency and volume of training. In various scenarios, protocols of the IMT has shown that best results are achieved with intensities ranging from 50 to 80% of the MIP, 2 times per day, with an average of thirty breathes in each session (sixty breaths per day)[18,22,26,32]. In fact, a load of 15% has been used in many studies as a placebo condition. The loading range between 15 and 50% has not been studied in detail. However a 30% load, with 300 repetitions per session, generates improvements in strength of only around half those elicited by 50% load, with 30 repetition twice a day, over a 4-week period of training[33].

The diaphragm is composed by only 55% of type I fibers[34], but because it works 24 hours per day, seven days a week, it has been thought that the diaphragm should receive endurance training (30% of MIP) to improve its performance[35]. However, it has been described, that during situations which leads to increased activity of inspiratory muscle recruitment, a change occurs with Type I to Type II fibers[36]. It is likely the change in the pattern of fiber recruitment occurs in difficult weaning patients when placed under stress during the spontaneous breathing test. Thus, there is a rationale to perform strength training for the inspiratory muscles when considering release from MV[7,18].

MIP can be used to determine the load used in IMT for patients under MV, but measurement of this marker has poor reproducibility and precision since it depends on the effort of patients (and often they cannot cooperate)[37]. The recommendations of the American Thoracic Society[27], based on Marini's et al.[38] protocol, suggests three measurements with an unidirectional valve, and a measuring time of 25 seconds, and this suggestion was consistently held by many researchers[17,19-21]. However, a recent study showed that it takes approximately 50 seconds of maneuver to reach the MIP[28]. With 25 seconds, only 75% of the real MIP was reached (figure 2). Based on this data, it can be said that the intensity of IMT employed by Cader et al. in both studies[17,20], e.g., may have been sub-optimal (22% of the MIP). Even with an increase of 10% per day, they may have taken on average 5 days to reach 50% of the real value of MIP. The same pattern can be seen at Condessa et al.[21] study.

Figura 2 | Inspiratory peaks at specific times. Adapted from de Souza et al[28].



Probably, because of this difficulty in achieving the real value of MIP, Martin et al.[18] used MIP measured according to the recommendation of the ATS[27] as a way of monitoring and not as a method for the definition of the load. A study protocol for inspiratory muscle training to promote recovery and outcomes in ventilated patients, recommended high intensity interval training that allows the subject to complete five sets of six breaths each session, performed daily on weekdays[32]. However, this must be tested in a RCT to prove its superiority.

What is the Best Time to Measure Treatment Effect?

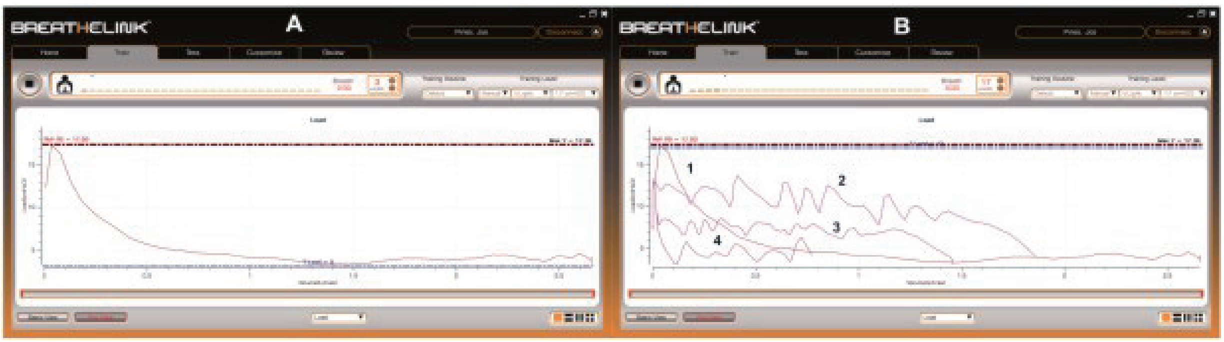
The time to measure the IMT effect is also important. Classical studies showed that is necessary at least ten days to increase strength in the limb muscles with minimal clinically important difference[39,40]. This is very similar to inspiratory muscles that are necessary at least fourteen days to have improvement on strength[41]. This early increasing on strength is related to neurological adaptation, hypertrophy starts to occur only from 20 day[40,41]. The increasing of diaphragm thickness (hypertrophy) was already demonstrated by Downey et al.[42] (8–12%) after 4 weeks of IMT set at 50% of MIP in healthy subjects.

All RCTs published in this field had on average less than 7 days of IMT[17,19-21] excluding Martin's et al.[18] study. This fact could have impaired the results.

Which Kind of Device Should Be Used to Carry Out Imt?

The biggest challenge in the training of mechanically ventilated patients is the use of conventional devices to impose loads on the respiratory muscles. When training starts, the patient must be disconnected from the ventilator and the respiratory monitoring is lost. A new class of device is now available that is possible to monitor respiratory variables during the training. One example of this is the POWERBreathe Kinect Series (POWERBreathe-HaB UK) an electronic kinetic device with feedback software that helps professionals to understand what is happening with patients during their training. This device provides automatically processed information on external inspiratory work. Moreover, power and breathing patterns during loaded breathing tasks is shown, thus the onset of fatigue can be detected earlier (figure 3). POWERBreathe Kinect Series was externally evaluated by Belgian researchers and they concluded that the Kinect technology provides automatically processed and valid estimates of physical units of energy during loaded breathing tasks[43]. Recently, de Souza et al.[44] published a case report showing good results using the same technology to train a prolonged mechanically ventilated patient.

Figura 3 | Fatigue onset detection.



Patient, 71 years old, undergoing IMT in MV. **A;** the first breath with a load of 3 cmH_2O, showing good performance. **B;** The next three breaths with the load of 17 cmH_2O, showing fatigue onset detected through saw pattern in breaths 2, 3 and 4.

Another great advantage of this kind of technology is the capacity of load adjustment (1 cmH_2O per 1 cmH_2O) reaching 3 to 200 cmH_2O. Beyond that, the device can adjust the load dynamically, imposing higher load at the beginning of inspirations and lower load close to vital capacity. Thus, a greater range of motion can be reached improving the effectiveness of the training.

What Are the Best Endpoints to Evaluate the Effect of Imt During the Process of Discontinuing Patients from MV?

The choice of adequately endpoints is fundamental to measure the impact of IMT on mechanically ventilated patients. The major endpoints used to patients undergoing mechanical ventilation are weaning time, weaning success, re-intubation rate, time spent on MV and mortality rate. A lot of confounding factors are present in intensive care setting. It is often difficult to consider the real influence of each variable in a given outcome[10]. The best way is to use outcomes with less influence of confounding factors.

Furthermore, is fundamental to understand the correct definitions for some results. For some time there has been confusion between the terms "weaning success" and "success of extubation". This has raised the need for use of other nomenclatures[31]. Success in weaning means that the patient performed well in the spontaneous breathing test without signs of respiratory distress and is able to be extubated[29,30]. Patients with successful extubation are those that continue breathing without

MV after being successfully weaned and tracheal tube removed for more than 48 hours without the need of any ventilatory support[31]. The misunderstanding of these definitions was well demonstrated by Tobin et al in a publication defending the RSBI[29]. The RSBI predicts successful weaning but it was questionably described in a guideline from the American Association for Respiratory Care, as a predictor of successful extubation[45].

While successful weaning rates appear to be directly linked to inspiratory muscle capacity[13,14], successful extubation is related to the ability to protect the airway and make bronchial hygiene, i.e., ability to cough[46,47]. Considering this information, perhaps the extubation success rate is not the best endpoint to measure the effectiveness of IMT, as used by Cader et al.[20]. Inspiratory capacity is directly linked to the ability to cough adequately, but isn't the major determinant of good airway protective performance.

Thus, inspiratory muscle strength, weaning time and weaning success should be utilized as primary outcomes. These are directly linked to IMT. Extubation success rate, re-intubation rate, time spent on MV and mortality, suffer impact of a lot of variables that can impair the measurement of IMT benefits.

Conclusion

This review demonstrated the necessity of new RCTs despite of some well designed RCTs have already been published. Many evidences point out that a high intensity training with loads ≥ 50% of MIP in 5 to 6 sets, aiming to reach thirty breathes, one or twice a day, seven days per week is a suitable protocol to improve performance on mechanical ventilation. Patients must be trained at least for two weeks in order to IMT promotes clinically significant effects. It is possible, that outcomes such as the onset of weaning process, duration and success on the weaning, have higher correlation with IMT. In conclusion, IMT on mechanically ventilated patients seems to be a promissory treatment despite controversial results. RCTs should be carried out to verify the efficacy of the high intensity training during a suitable period of training using electronic kinetic devices in mechanically ventilated patients.

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