Respiratory muscle dysfunction in respiratory and non-respiratory diseases: clinical and therapeutic approaches.

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“No hay que temer a nada en la vida, solo hay que comprender”

Maria Curie

Dedico este proyecto a mis queridos padres y hermano (Sergio, Maria y Bruno), a mi compañero Héctor, a mis tutoras Ester y Esther, y a mi jefe Ferran

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ABSTRACT

Objective: Respiratory muscle dysfunction, a clinical condition that may be present in both respiratory and non-respiratory diseases, can negatively affect patients' functional outcomes. The aim of this project was to determine if the increase in respiratory muscle strength after inspiratory and expiratory muscle training (IEMT) is associated with an improvement in clinical outcomes of patients with varying diseases.

Methods: Three randomized clinical trials evaluated the effectiveness, feasibility, and safety of respiratory muscle training in patients with non-respiratory diseases: Study #1 randomly assigned 22 patients with chronic heart failure (CHF) to 4-week high-intensity inspiratory muscle training (hi-IMT) or sham IMT (control); Study #2 randomly assigned 109 subacute patients after a first ischemic stroke to IEMT or sham IEMT study groups along with a standard multidisciplinary inpatient rehabilitation program; Study #3 assessed the impact of high-intensity respiratory muscle training in combination with aerobic exercise training on exercise capacity, respiratory muscle strength, and quality of life in 37 patients with non-small cell lung cancer (NSCLC) after lung resection, compared to controls (usual aerobic exercise training).

Results: Study #1: The hi-IMT group showed a significant improvement in both strength and endurance. Inspiratory muscle strength increased 57.2% in the intervention group, compared with 25.9% in the control group ($p<0.001$), and endurance increased 72.7% and 18.2%, respectively ($p<0.001$). No adverse effects occurred during the intervention. Study #2: IEMT was associated with significantly improved inspiratory and expiratory muscle strength: effect size d= 0.74 (95%C I 0.28 to 1.20) and d= 0.56 (95%CI 0.11 to 1.02), respectively. Respiratory complications at 6 months occurred more frequently in the control group (8 vs 2, p= 0.042), with an absolute risk reduction of 14%. No major adverse events or side effects were observed. Study #3: The 8-week training program significantly improved peak work rate (□15.1, 95%CI 2.7 to 27.5) and maximal inspiratory and expiratory pressures (□18.2 [95%CI 5.5 to 30.9], and 12.0 [95%CI 2.2 to 21.7], respectively), compared to controls.

Conclusions: Respiratory muscle training was shown to be an effective, feasible and safe tool to improve respiratory muscle function in patients with CHF, subacute stroke and surgically treated lung cancer. Furthermore, IEMT could potentially be used to reduce respiratory complications in stroke patients. In NSCLC patients after lung resection, IEMT combined with aerobic exercise improved peak work rate and respiratory muscle strength. These findings provide a good rationale for clinicians and healthcare workers to encourage respiratory muscle training in the management of diverse clinical conditions.

Key-words: Respiratory muscles, respiratory muscle training, chronic heart failure, stroke, lung cancer.

RESUMEN

Objetivos: La disfunción muscular respiratoria es una condición clínica que puede estar presente en enfermedades respiratorias y no-respiratorias, comprometiendo la capacidad funcional de los pacientes. El objetivo principal de este proyecto fue determinar si el incremento en la fuerza muscular respiratoria tras entrenamiento muscular inspiratorio y espiratorio (IEMT) se asocia a una mejoría clínica en diferentes enfermedades.

Métodos: Tres ensayos clínicos randomizados valoraron la efectividad, factibilidad y seguridad del entrenamiento muscular respiratorio en pacientes con enfermedades no-respiratorias. **≠Estudio 1:** Veintidós pacientes con insuficiencia cardíaca fueron randomizados a 4 semanas de entrenamiento respiratorio de alta intensidad o a entrenamiento placebo. **≠Estudio 2:** Ciento nueve pacientes tras primer episodio de ictus fueron randomizados a IEMT o a entrenamiento respiratorio placebo junto con programa de rehabilitación multidisciplinar hospitalario estándar**. ≠Estudio 3**: se estudió el impacto del IEMT de alta intensidad en combinación con entrenamiento aeróbico en la capacidad de ejercicio, fuerza muscular respiratoria y calidad de vida en 37 pacientes con cáncer de pulmón de células no pequeñas tras cirugía de resección pulmonar, en comparación al grupo control que realizó protocolo de rehabilitación estándar.

Resultados: **≠Estudio 1:** Tras entrenamiento inspiratorio de alta intensidad se observó mejoría significativa en la fuerza y en la resistencia muscular respiratoria. La fuerza muscular inspiratoria aumentó un 57.2% en el grupo intervención en comparación con un 25.9% en el grupo placebo, y la resistencia aumentó un 72.7% y 18.2%, respectivamente. **≠Estudio 2:** El IEMT se asoció con una mejoría significativa de la fuerza muscular inspiratoria y espiratoria. El tamaño del efecto de la intervención fue d= 0.74 (95%IC 0.28 a 1.20) y d=0.56 (95%IC 0.11 a 1.02) respectivamente. **≠Estudio 3:** Se observó una mejoría significativa en la carga de trabajo pico (□15.1, 95%CI 2.7 a 27.5) y en la presión inspiratoria máxima (□18.2, 95%CI 5.5 a 30.9) y en la presión espiratoria máxima (12.0, 95%CI 2.2 a 21.7) tras la realización de un programa de ejercicios de 8 semanas de duración.

Conclusiones: Se demostró que el IEMT es una herramienta terapéutica efectiva, factible y segura para mejorar la función muscular respiratoria en pacientes con insuficiencia cardiaca, ictus subagudo y quirúrgicamente tratados por cáncer de pulmón. Además, el IEMT puede ser potencialmente utilizado en pacientes con ictus con el objetivo de disminuir el número de complicaciones respiratorias a largo-plazo. El IEMT en conjunto con un protocolo de ejercicio aeróbico ha demostrado mejorar la carga pico de trabajo y las presiones respiratorias máximas en pacientes con cáncer de pulmón sometidos a cirugía de resección. Estos hallazgos proporcionan una buena justificación a clínicos y profesionales sanitarios a fomentar el uso del IEMT en el manejo clínico de estos pacientes crónicos con diferentes afecciones clínicas.

Palabras-clave: Músculos respiratorios, entrenamiento muscular respiratorio, insuficiencia cardiaca, ictus, cáncer de pulmón.

PREFACE

Respiratory muscle dysfunction is a clinical condition that may be present in both respiratory and non-respiratory diseases. This impairment of muscle function can have a negative effect on clinical outcomes, contributing to a further worsening of the patient's clinical condition.

This doctoral thesis has been directed by the 'Rehabilitation Research Group' (RERG) in collaboration with the Muscle Wasting and Cachexia in Chronic Respiratory Diseases and Lung Cancer Group (Lung Cancer and Muscle Research Group) of the Institut Hospital del Mar d'Investigacions Mèdiques (IMIM) in Barcelona. Muscle dysfunction has been a priority area of research in these groups from different perspectives: exercise and muscle training in the RERG, Physiopathology and Molecular Biology in the Lung Cancer and Muscle Research Group. The large number of published studies in journals with high impact factor endorses the quality and leadership of these research groups.

The groups' first investigations in patients with non-respiratory diseases were carried out in 2010. A pilot study showed the effectiveness of inspiratory muscle training (IMT) in heart failure patients, using a modified IMT device. At the same time, a new respiratory muscle training (RMT) device (Orygen Dual®) was being developed in our institution. The Orygen Dual valve® was finally patented in 2011, and the RERG decided to reproduce the previous study using this new device.

Up to then, research on RMT had focused on patients with chronic obstructive pulmonary disease, but had been scarcely addressed in other conditions. In the last 5 years, the RERG has aimed to study the effects of RMT in other respiratory diseases (bronchiectasis, lung cancer) and in non-respiratory diseases. The study of respiratory muscle dysfunction in stroke patients has made it possible to start an increasing collaboration with neurorehabilitation researchers, in which RMT plays a role in the management of patients with dysphagia.

1. SCIENTIFIC COLLABORATIONS

Study# 1: Respiratory Rehabilitation Unit in collaboration with the Cardiology Department (Hospital del Mar, Barcelona).

Study# 2: Respiratory Rehabilitation Unit in collaboration with the Neurorehabilitation Unit (Parc de Salut Mar).

Study #3: Respiratory Rehabilitation Unit in collaboration with the Thoracic Surgery and Pulmonology departments (Parc de Salut Mar and Hospital de Sant Pau).

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COMMUNICATIONS

Preliminary results of this project have been presented in national and international conferences:

- The INCA Study: Respiratory muscle weakness in patients with chronic heart failure and the effects of a heavy duty training of inspiratory muscles.
  Marco E, Ramírez-Sarmiento AL, Coloma A, Comin J, Martínez-Llorens JM, Boza R, Guillen A, Belmonte R, Gea J, Orozco-Levi M.
  Presented at the 5th World Congress of the International Society of Physical and Rehabilitation Medicine. June 2009, Istanbul, Turkey.

- The INCA Study: Respiratory muscle weakness in patients with chronic heart failure, effects of heavy duty training.
  Ramírez-Sarmiento AL, Marco E, Coloma A, Comin J, Martínez Llorens, Escalada F, Gea J, Orozco-Levi M.
  Presented at the XXVIII Diada Pneumològica de la Societat Catalana de Pneumologia. March 2010, Girona, Catalonia, Spain.

- Dual respiratory muscle training in patients with subacute stroke.
  Depolo M, **Messaggi-Sartor M**, Donaire MF, Guillén-Solà A, Barrera de Paz C, **Marco E.**
  Presented at the 51º Congreso de la Sociedad Española de Rehabilitación y Medicina Física. May 2013. Salamanca, Spain.

- Respiratory muscle training in subacute stroke patients: a randomized clinical trial.
  Messaggi-Sartor M, Depolo M, Donaire MF, Alvarado M, Duarte E, Guillén-Solà A, Orozco-Levi M, Barrera MC, Pascual E, Rodríguez DA, Bofill N, Escalada R, Orozco-Levi M, Duarte E, Marco E.
  Presented at the Annual Congress of the European Respiratory Society. September 2013, Barcelona, Catalonia, Spain.

- Respiratory muscle training in subacute stroke patients: a randomized clinical trial.
  Messaggi-Sartor M, Guillén-Solà A, Depolo M, Galindo M, Rodríguez DA, Escalada R, Marco E.
  Presented at the 9th World Stroke Congress, October 2014, Istanbul, Turkey.

- Inspiratory and Expiratory Muscle Training in Subacute Stroke patients: a randomized clinical trial.
  Messaggi-Sartor M, Guillén-Solà A, Depolo M, Duarte E, Rodríguez DA, Barrera MC, Barreiro E, Villanueva-Sánchez H, Escalada F, Orozco-Levi M, Marco E.
  Presented at 25ena Jornades d'Actualització en Rehabilitació i Medicina Física. March 2015, Tarragona, Catalonia, Spain. Award best scientific presentation.

- Impact of lung resection surgery on peak oxygen uptake and muscle strength in non-small cell lung cancer patients.
  Messaggi-Sartor M, Chiarella S, Rodríguez A, Martínez E, Palomares C, Muniesa JM, Güell RM, Marco E.
  Presented at the European Respiratory Society Annual Congress 2015, Amsterdam, Netherlands.

- The impact of an exercise intervention plus high-intensity respiratory muscle training on exercise capacity and respiratory muscle strength in patients with non-small cell lung cancer submitted to lung resection surgery.
  Messaggi-Sartor M, Chiarella S, Rodríguez A, Martínez E, Palomares C, Muniesa JM, Güell MR, Marco E.
  Presented at the 26ena Jornades d'Actualització en Rehabilitació i Medicina Física. May 2016, Barcelona, Catalonia, Spain. Award best scientific presentation.

- The impact of an exercise intervention plus high-intensity respiratory muscle training on exercise capacity and respiratory muscle strength in patients with non-small cell lung cancer submitted to lung resection surgery.
  Messaggi-Sartor M, Chiarella S, Rodríguez A, Martínez E, Palomares C, Muniesa JM, Güell RM, Marco E.
  Presented at the 54º Congreso de la Sociedad Española de Medicina Física y Rehabilitación. June 2016, Málaga, Spain. Award best scientific presentation.

Other publications related with this project

- Guillén-Solà A, Marco E, Martínez-Orfila J, Donaire-Mejías MF, Depolo Passalacqua M, Duarte E, Escalada F. Usefulness of the volume-viscosity swallow test for screening dysphagia in subacute stroke patients in rehabilitation income. NeuroRehabilitation. 2013; 33(4):631-8.

- Guillén-Solà A, Chiarella SC, Martínez-Orfila J, Duarte E, Alvarado-Panesso M, Figueres-Cugat A, Bas N, Marco E. Usefulness of citric cough test for screening of silent aspiration in subacute stroke patients: a prospective study. Arch Phys Med Rehabil. 2015 Jul; 96(7):1277-83.

- Guillén-Solà A, **Messaggi-Sartor M**, Bofill Soler N, Duarte E, Barrera MC, Marco E. Respiratory muscle strength training and neuromuscular electrical stimulation in subacute dysphagic stroke patients: A randomized controlled trial Clin Rehabil. 2016 Jun 7.

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ABBREVIATIONS

10 RM:	Ten maximal repetitions
6MWT:	Six-minute walking test
CHF:	Chronic heart failure
COPD:	Chronic obstructive pulmonary disease
EMT:	Expiratory muscle training
HRQoL:	Health-related quality of life
IEMT:	Inspiratory and expiratory muscle training
IMT:	Inspiratory muscle training
MLHFQ:	Minnesota living with chronic heart failure questionnaire
MVC:	Maximal voluntary contraction
NSCLC:	Non-small cell lung cancer
Pdi:	Transdiaphragmatic pressure
PEmax:	Maximal expiratory pressure
Pgas:	Gastric pressure
PImax:	Maximal inspiratory pressure
Pnas:	Nasal pressure
Poes:	Esophageal pressure
PPC:	Post-operative pulmonary complications
RMT:	Respiratory muscle training
SAP:	Stroke-associated pneumonia
SD:	Standard deviation
SF-36:	Short-Form health survey
SNIP:	Sniff nasal inspiratory pressure
TLC:	Total lung capacity
VATS:	Video-assisted thoracoscopy surgery
VO2peak:	Peak oxygen uptake

Figures List

1. INTRODUCTION

1.1 Anatomic overview of respiratory muscles

The respiratory system consists essentially of two parts: the lungs (a gas-exchanging organ) and a muscular pump that ventilates the lungs through coordinated activity of the inspiratory and expiratory muscles (1). Inspiratory muscles are responsible for airflow generation. The main inspiratory muscle is the diaphragm, a dome-shaped muscle inserted into the lower ribs. The phrenic nerve supplies this muscle from cervical segments 3, 4 and 5 (2).

The diaphragm has two functionally distinct parts: the crural and the costal (Figure 1). Contraction of the crural part of the diaphragm displaces both rib cage and abdomen while inflating the lung. However, a contraction of the costal part of the diaphragm has no direct effect on the rib cage, because it lacks attachments to the rib cage, but promotes a displacement of the abdominal viscera (1).

When the diaphragm contracts, the abdominal content is forced downward and forward and promotes a change in intrathoracic pressure that allows air to enter the lungs. Other muscles that progressively participate in the inspiration as ventilatory demands increase are external intercostal muscles and accessory muscles of inspiration. External intercostal muscles connect adjacent ribs and slope downward and forward; when they contract, the ribs are pulled upward and forward, increasing both the lateral and antero-posterior diameter of the thorax. The accessory muscles of inspiration include the scalene muscles, which elevate the two ribs, and sternocleidomastoids, which raise the sternum (2).

The most important expiratory muscles are those of the abdominal wall, including the rectus abdominis, internal and external obliques and transverses abdominis muscles. When abdominal muscles contract, intra-abdominal pressure is raised and the diaphragm is pushed upward. These muscles also contract forcefully during coughing, vomiting and defecation. Expiration is a passive process and expiratory muscles assist expiratory flow. If additional effort is required to exhale, such as during exercise or with respiratory disorders, the expiratory muscle group contracts, increasing the alveolar-atmosphere pressure gradient. The intercostal muscles assist active expiration by pulling the ribs downward and inward, thus decreasing the thoracic volume (2-3).

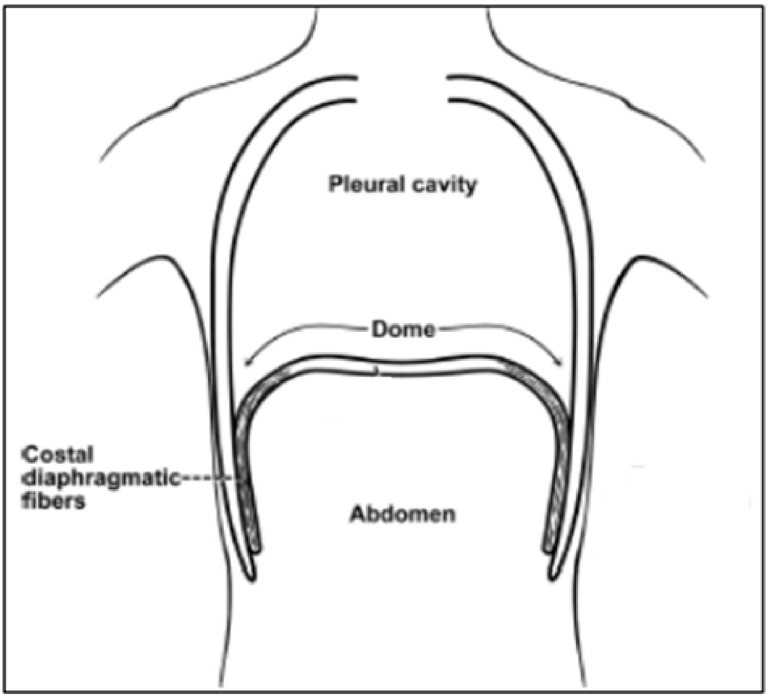

Figure 1: The diaphragm

Adapted from: *De Troyer A, Wilson T. J Appl Physiol, 2016*

1.2. Functional properties of respiratory muscles

Respiratory muscles are essentially striated muscles that contract against resistive airways and against elastic recoil (chest wall and lungs). Their resting position is uniquely determined by a balance of recoil forces of the lung and chest wall. Respiratory muscle contractions are rhythmic and their action is life-sustaining (4-6).

Strength and endurance are the main functional properties of the respiratory muscles. Strength is defined as the ability to develop a brief maximal effort and endurance is the ability to maintain a submaximal contraction over time. Strength depends on muscle mass, muscle length, innervation, fibre size and the number of anaerobic fibbers. Endurance is related to the aerobic properties of the muscle that are coordinated by capillary density, proportion of type I fibbers and enzyme activity in the oxidative pathways (3).

Based on metabolic properties, respiratory muscle fibbers are classified into three categories:

- Type I: slow-oxidative, fatigue resistant and adapted for sustained activity requiring submaximal tension generation;
- Type IIb: fast-glycolitic, fatigue sensitive and adapted for short bursts of near-maximal activity;
- Type IIa: fast-oxidative-glycolytic, fatigue resistant and intermediate in size and myoglobin content.

The diaphragm contains approximately 80% of fatigue resistant fibbers, compared with 40% in limb muscles (4, 7-9). The fibre type composition of muscle determines the contractile response. Those muscles with type I predominance are more likely to tolerate sustained and low intensity efforts. Muscles rich in type II fibbers are capable of high-powered but not sustainable work. Respiratory muscles have a mixture of both fibre types that allows fatigue resistance, necessary for unceasing function and high-powered bursts needed for exercise and coughing. Factors that may change fibre composition include aging, disuse, training and chronic respiratory loading. Type I atrophy impairs endurance, whereas type II atrophy reduces strength (8, 10-13).

1.3 Assessment of respiratory muscle function

The main function of the respiratory muscles is to develop force, usually estimated as pressure, and to shorten as lung volumes change or chest wall structures are displaced. Thus, to characterize respiratory muscle function it is important to take into account lung volume displacements and pressures. Assessments of respiratory muscle pressure should be viewed as indices of “muscle output” rather than direct measurements of contractile properties of the muscle.

Conventional respiratory function tests are not specific to detect any impairment in respiratory muscle function, but nonetheless could give useful information about respiratory muscle performance. Research output in this area has progressively increased, in an effort to address the limitations of these tests. In 2003 a committee of experts reviewed the merits of the available evaluation techniques and published a statement addressing the major aspects of respiratory muscle function (14).

For most patients, the suspicion of clinically important respiratory muscle weakness may be confirmed or excluded by simple tests that can be performed in the general hospital setting without the purchase of expensive equipment, but more complex tests in a specialized laboratory could be useful in some patients (Figure 2) (15).

Several methods are available to assess respiratory muscle strength during inspiratory and expiratory phases. These methods are divided into two categories: volitional and non-volitional tests.

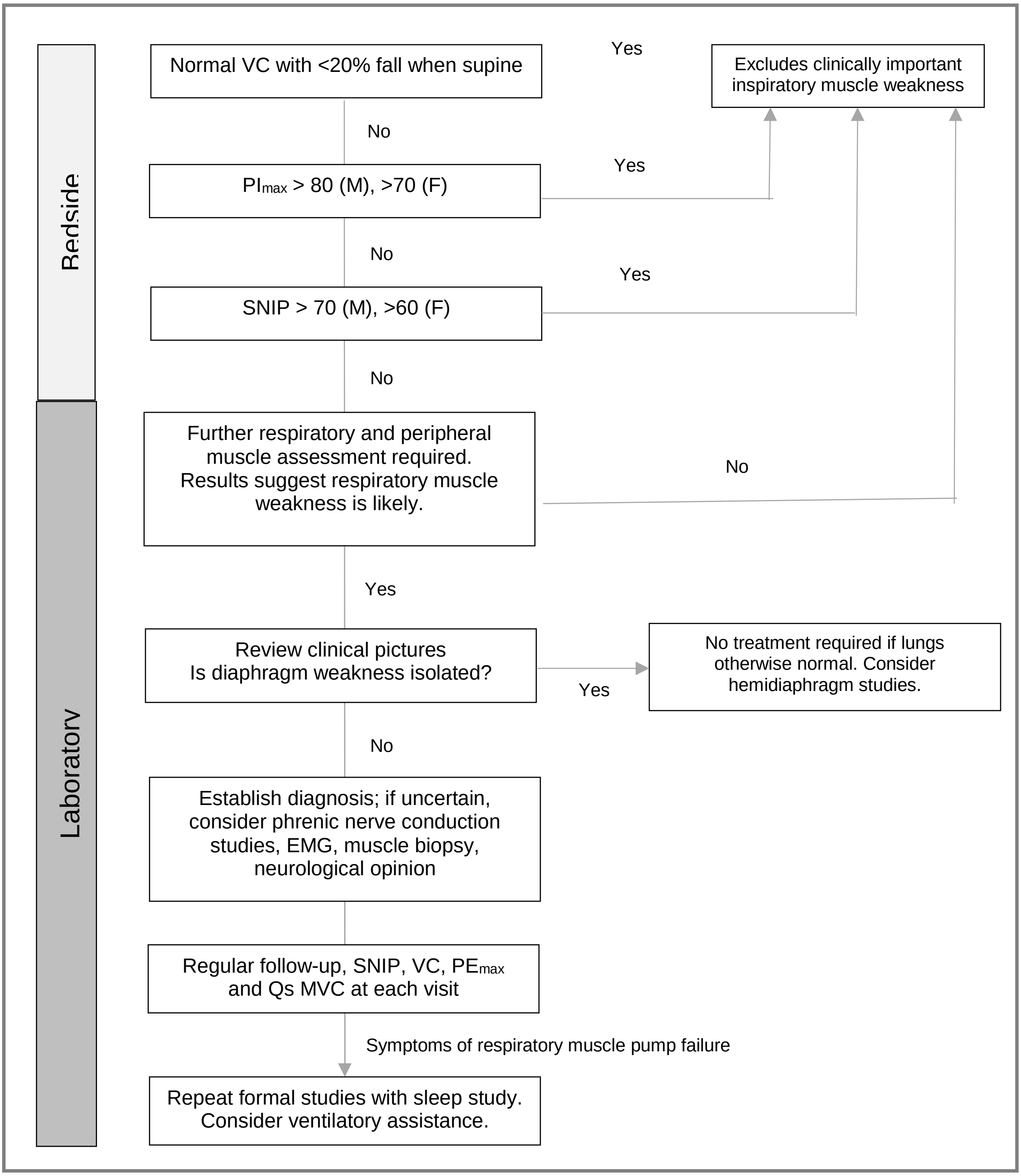

Figure 2. Algorithm to assess respiratory muscles

VC: vital capacity; **MIP**: maximal inspiratory pressure; **MEP**: maximal expiratory pressure; **SNIP**: sniff nasal inspiratory pressure; **Qs**: quadriceps muscle; **MVC**: maximum voluntary contraction force

Adapted from *Polkey MI et al., Thorax 1995*.

1.3.1 Evaluation of respiratory muscle strength

- **Volitional tests**

The measurement of maximal inspiratory and expiratory pressures (PImax and PEmax, respectively) at the mouth is a volitional method widely used to assess global inspiratory and expiratory muscle strength (15). It has the advantage of being non-invasive, easy to perform and well tolerated by patients. The recent development of hand-held pressure meters means the technique can now be easily used at the bedside, and normal cut-off values have been established for different populations worldwide (16-21).

Assessment of maximal respiratory pressures at the mouth

Methodology: The ATS/ERS Statement on Respiratory Muscle Testing proposed a standardized approach to test PImax and PEmax. A flanged mouthpiece is attached to a short, rigid tube with three-way tap or valve system to allow normal breathing followed by either a maximum inspiratory or expiratory manoeuvre. However, this must be held tightly around the lips, to prevent leaks. The system requires a small leak to prevent glottis closure during the PImax manoeuvre and to reduce the use of buccal muscles during the PEmax manoeuvre. Ideally, the inspiratory and expiratory pressures should be sustained for 1.5 seconds, so that the maximum pressure sustained for one second can be recorded (14).

The test should be performed by an experienced operator, who should strongly urge subjects to make a maximum inspiratory and expiratory effort at or near residual volume (RV) and total lung capacity (TLC), respectively. Subjects are normally seated and often need coaching to prevent air leaks around the mouthpiece and to support the cheeks during the expiratory effort. Once the operator is satisfied, the maximum value of three manoeuvres varying by less than 20% is recorded; however, low variability may not guarantee that maximal efforts have been made (14).

Disadvantages: Volitional tests require full patient cooperation. A low result is difficult to interpret, may be due to lack of motivation and does not necessarily indicate reduced inspiratory or expiratory muscle strength. In such circumstances, it would be appropriate to undertake more detailed studies.

Clinical applicability:

- **PI_{max}:** The measurement of inspiratory muscle strength can aid the differential diagnosis of dyspnoea (22) and assessment of response to cardiopulmonary physiotherapy and rehabilitation, prescribing and monitoring RMT and assessing the possibility and success of weaning critically ill patients from mechanical ventilation (23-24). High PImax values (PImax >80cmH20) provide useful information, excluding clinically important respiratory muscle weakness (15).

- **PE_{max}:** Its major use is to assess cough strength. Expiratory muscle weakness correlates with respiratory infections (25).

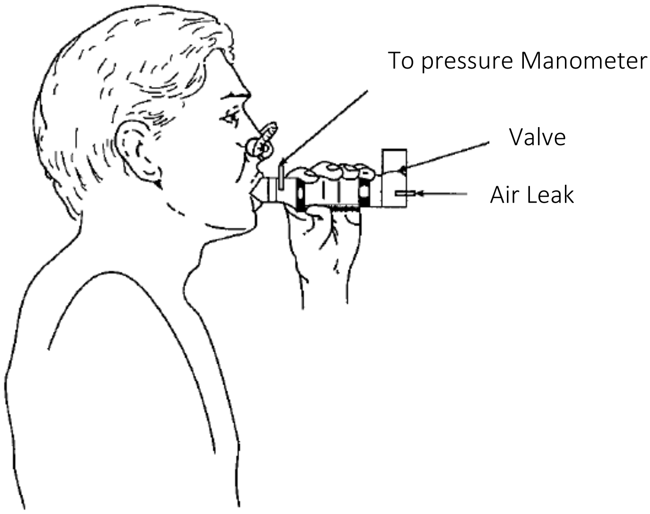

Figure 3. Measurement of maximal static respiratory pressures.

Adapted from: *(ATS/ERS Statement on respiratory muscle testing. AMRCCM 2002).*

Sniff nasal inspiratory pressure

This short, sharp voluntary inspiratory manoeuvre is performed through one or both unclouded nostrils. Maximal sniffs have been widely used and validated as reproducible and reliable tests of diaphragm or global respiratory muscle strength (26).

The sniff is a natural manoeuvre that is easier to perform than static efforts. Patients should be instructed to sit or stand comfortably, and to make sniffs using maximal efforts starting from a relaxing expiration. Most individuals achieve a plateau of pressure value within 5-10 attempts.

The SNIP can be helpful when deciding whether to pursue the reason for a low PI_{max} and can be performed at the bedside (29).

Normal SNIP values have been established (men >70 cmH_20, women >60 cmH_2O) (27).

Non-volitional tests

For some patients, simple non-invasive tests will discard the possibility of respiratory muscle weakness. For patients with known weakness, a precise estimation of the weakness is sometimes important to make care management decisions.

To assess respiratory muscle strength using non-volitional tests, oesophageal, gastric balloons must be placed, using topical anaesthesia (15). This is an invasive method that could be uncomfortable for the patient, and requires the use of specific and expensive equipment by an experienced examiner. These tests have been used mostly in research settings. Considering that all these factors are not always available in clinical settings, this project focused on volitional tests to assess respiratory muscle strength. In addition, the present project aimed to contribute results that could be applied in clinical practice. Specific information about non-volitional tests can be found in the ERS Statement (14).

In summary, proper assessment of respiratory muscle strength depends on the use of appropriate tests. Figure 4 summarizes the cut-off values for the diagnosis of weakness for each respiratory muscle test. In the absence of non-volitional assessments, a combination of non-invasive procedures (PI_{max} and SNIP) can substantially increase the precision of the diagnosis (28).

TEST	SEX	CALCULATION	CUT OFF (CMH_2O)	ROUNDED (CMH_2O)
PIMAX	**Male**	10.4-1.96 x 3.0 kPa	44.8	45
	Female	7.2-1.96 x 2.1 kPa	31.6	30
SNIFF POES	**Male**	105-1.96 x 26 cmH_2O	54.0	55
	Female	92-1.96 x 22 cmH_2O	48.9	50
SNIFF PNASAL	**Male**	0.91 x 55 cmH_2O	50.1	50
	Female	0.91 x 50 cmH_2O	45.5	45
SNIFF PDI	**Male**	148-1.96 x 24 cmH_2O	101.0	100
	Female	121-1.96 x 5 cmH_2O	72.0	70
TWITCH PDI	**Male**	28-1.96 x 5 cmH_2O	18.2	18
	Female	28-1.96 x 5 cmH_2O	18.2	18
PEMAX	**Male**	14.4 – 1.96 x 3.3 kPa	80.5	80
	Female	9.1 – 1.96 x 1.6 kPa	61.1	60
COUGH PGAS	**Male**	214.4 – 1.96 x 42.2 cmH_2O	131.7	130
	Female	165.1 – 1.96 x 34.8 cmH_2O	96.9	95
TWITCH T10	**Male**	x=1.6 – 1.96 x 0.20	16.1	16
	Female	x=1.6 – 1.96 x 0.20	16.1	16

Figure 4. Cut off values for the diagnosis of weakness for each respiratory muscle test.

PI_{max}: maximal inspiratory pressure; **P_{oes}:** oesophageal pressure; **P_{nasal}:** nasal pressure; **P_{di}**: transdiaphragmatic pressure; **PE_{max}**: maximum expiratory pressure; **P_{gas}**: gastric pressure.

Adapted from: *Steier J, et al. Thorax. 2007.*

1.3.2. Evaluation of respiratory muscle endurance

Endurance is the ability to sustain a level of minute ventilation or a level of inspiratory and expiratory pressures. The energy requirements of a working muscle are determined largely by the tension developed over time (tension-time product) and the rate of mechanical load being performed. The pressure-time product (PTI) is the integration of respiratory pressure over time. Furthermore, PTI describes the pressure-generating activity of the muscles, independent of a specific breathing rhythm, breathing frequency, or type of load within the experimental limits tested (14).

The most common endurance tests reported in the medical literature are the following:

- **Ventilatory endurance tests.** Maximal sustainable ventilation (MSV) is expressed as a percentage of 12 seconds of maximum voluntary ventilation (MVV). Two approaches are available to determine MSV: maximum effort technique (the subject seeks to sustain ventilation at a target level of 70-90% MVV for 8 minutes) and maximum incremental technique (starting at 20% MVV, the target ventilation is increased by 10% every 3 minutes). Limited data on normal MSV are available, and show considerable variability.
- **Endurance to external loads.** The external load can be resistive (the pressure required depends on flow), elastic (pressure depends on tidal volume), threshold (finite pressure required to open the valve, which is independent of flow and volume), or isoflow (flow rate held constant). The most widely used technique is that of threshold loading. Either the maximum

sustainable threshold load or the maximum incremental threshold load can be measured. The incremental threshold loading test, which uses the same principles as an incremental exercise test, is the most commonly undertaken, but available normal data are limited.

- **Maximum Incremental Threshold Loading:** The subjects inspire from a threshold valve, beginning at initial threshold pressures of approximately 30-40% of PI_{max}. Threshold pressure is then increased by a unit of weight (e.g., 100 g) added to the outside of the valve, resulting in a change in pressure of approximately 5-10% of PI_{max}, until the load cannot be tolerated for 2 minutes. The maximum inspiratory mouth pressure tolerated for the full 2-minute interval is considered the peak pressure (P_{peak}). This test is the most commonly used to assess endurance of inspiratory muscles (14).

1.4. Respiratory muscle dysfunction

1.4.1. Definition and physiological concepts

Muscle dysfunction can be defined as reduced muscle strength and/or endurance. Muscle dysfunction can be expressed as fatigue or weakness. **Fatigue** is a state in which the muscle is temporarily unable to perform its current tasks; this condition is reversible with rest, thus differing **weakness**, which is a much more permanent impairment in muscle contractile properties. Although fatigue and weakness appear to be very different conditions, they are related in the sense that a weak muscle more easily becomes fatigued. Various conditions, and not only diseases, can result in muscle dysfunction. Some involve striated muscle structure directly while others primarily affect the structures of the nervous, vascular and osteoarticular systems (29). Dysfunction of both respiratory and limb muscles in COPD has been studied in depth, and seems to be caused by the complex interaction of general (inflammation, impaired gas exchange, malnutrition, morbidity, drugs) and local factors (changes in respiratory mechanics and muscle activity, and molecular events).

Respiratory muscles are contractile elements that have specific physiological functions such as body movement and generation of air and blood flow. **Dysfunction of inspiratory muscles** will result in hypoxemia and hypercapnia, and in ventilated patients can lead to difficulties in the weaning process. **Malfunction of expiratory muscles** will, in turn, give rise to difficulties upon exertion, coughing and attempts to expectorate secretions from the airways. A large number of studies have demonstrated that respiratory muscle function can also be impaired in widely diverse disorders other than COPD: chronic heart failure, cystic fibrosis, bronchial asthma, kyphoscoliosis, and neuromuscular diseases as well as muscle weakness and sepsis in intensive care units (3). The most common disorders that affect respiratory system and consequently respiratory and/or peripheral muscles are detailed in Figure 5 (3).

Respiratory System and muscle Dysfunction

Respiratory Disorder, frequent comorbidities and drugs known to alter muscle structure and function.

Respiratory disorders:

- Chronic obstructive pulmonary disease
- Bronchial asthma
- Sleep apnea-hypopnea and related syndromes
- Cystic fibrosis
- Scoliosis and other thoracic deformities
- Idiopathic pulmonary hypertension

Other conditions:

- ICU muscle weakness- deleterious effects of mechanical ventilation.
- Lung cancer (cachexia)

Frequent comorbidities:

- Chronic heart failure
- Sepsis
- Diabetes mellitus
- Aging – Sarcopenia

Drugs:

- Corticosteroids
- Anagonists of β- adrenergic receptors
- Statins
- Diuretic drugs
- Phosphodiesterase 5 inhibitors

Fig. 5. Respiratory disorders, comorbidities and drugs associated with muscle dysfunction.

Adapted from: *Gea J, et al. 2012.*

1.4.2. Respiratory muscle dysfunction in diseases other than chronic obstructive pulmonary disease

- **Chronic heart failure**

Chronic heart failure (CHF) is a clinical syndrome in which the heart is not able to provide tissue perfusion due to structural and/or functional abnormalities. These patients have exercise intolerance and dyspnoea, factors that are implicated in their limited exercise response and quality of life as well as in poor prognosis (30).

The mechanisms responsible for their limited exercise response include (but are not limited to) abnormalities in physiological response to exercise, skeletal muscle dysfunction and inspiratory muscle weakness. In addition, the impairment of respiratory muscle strength in these patients is correlated with lower peak oxygen uptake (VO_{2peak}), lower 6 minutes-walking distance (6MWD) and greater disease severity (30-33).

Between 30% and 50% of CHF patients have inspiratory muscle weakness, arbitrarily defined as PI_{max} less than 70% of the predicted value (34). The precise cause of respiratory muscle dysfunction remains speculative; it appears to be a consequence of the increase in ventilatory response to metabolic demands resulting in increased recruitment of respiratory muscles (32). Respiratory muscle biopsies have shown increased oxidative and lipolytic enzymatic activity and reduced glycolytic activity (35-37). In addition, there is a shift from fast to slow myosin heavy-chain isoforms, probably induced by myogenic regulatory factors as a likely adaptation to the increased effort of breathing (38-39). These abnormalities may contribute to the reduction of inspiratory muscle contractility. It was reported that CHF patients with inspiratory muscle weakness elicit a premature and more dramatic reduction in peripheral blood flow, resulting in the existence of respiratory muscle metaboloreflex (40). It appears that impaired delivery of oxygen to the diaphragm combined with increased inspiratory muscle work accumulates metabolites in the inspiratory muscles. This increase in metabolites stimulates type IV nerve endings, resulting in an exaggerated sympathetic-mediated vasoconstriction and reduced peripheral blood-flow (Figure 6) (41-48).

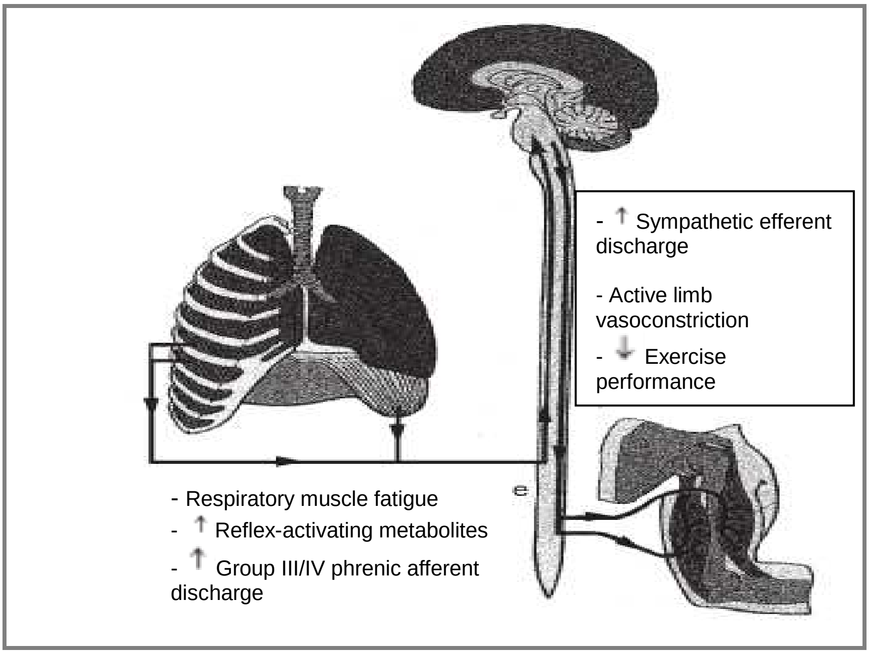

Figure 6. The major components and effects of the respiratory muscle metaboloreflex. Sheel AW *et al.* demonstrated that the respiratory-limb reflex has the ability, at least under resting conditions, to reduce significantly limb blood flow and vascular conductance (45).

Adapted from: *Seals D. J. Physiol, J Physiol. 2001*

- **Stroke**

The muscles used in breathing can be controlled voluntarily or automatically. The pyramidal tract is responsible for voluntary control of breathing and the bulbospinal tract for the automatic control (Figure 7) (49). The pyramidal motor neurons for respiration are spread over a large area of the cortex. For that reason, most cerebrovascular accidents do not cause significant impairment of respiratory muscles (49-50). In contrast, cerebral infarcts in the internal capsule can cause extensive damage to the pyramidal respiratory fibbers, because the pyramidal fibbers become densely aggregated.

Stroke adversely affects respiratory muscle function and chest wall kinematics. In 1981, De Troyer *et al.* (51) reported a striking reduction in electromyography activity of both intercostal muscles and the diaphragm during voluntary inspirations in the paretic side after a stroke event. Przedborski *et al.* reported that respiratory drive was abnormal in the hemiplegic side and the function of the intercostal muscles was affected specifically during voluntary hyperventilation (52). Patients with capsular lesions had asymmetrical latencies for each hemidiaphragm (responses were markedly delayed or absent in the paralyzed side throughout cranial magnetic stimulation).

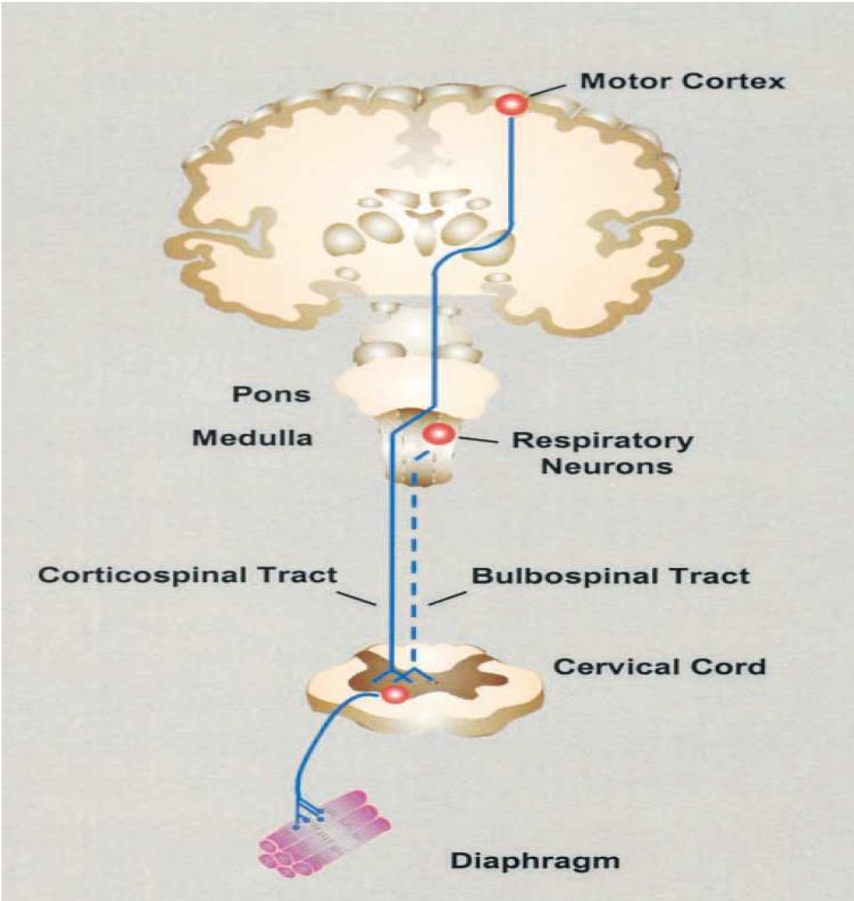

Figure 7: Voluntary (cortical tract) and automatic (bulbospinal tract) pathways that control breathing. Motor fibers of the corticospinal tract originate in the cerebral cortex, cross over in the medulla, and descend in the spinal cord. Motor fibers of the bulbospinal tract in the respiratory neurons of the medulla cross over at or near the upper cervical cord, and descend in the spinal cord.

Similowski T, et al. Am J Respir Crit Care Med 1996.

Early reports show that hemiplegia caused by a lesion above the brain steam induces reductions on whole hemithorax movement during deep voluntary breathing (53-54). These findings were confirmed 30 years later by Cohen *et al.* (55) in a study of the effects of lesions above the brain stem on volitional breathing in a group of hemiplegic patients. Using ultrasonography during both spontaneous and voluntary breathing at similar tidal volumes, Cohen et al concluded that stroke patients have reductions in diaphragmatic excursion on the affected side during volitional breathing. One consideration to take into account concerning these findings is that the two hemidiaphragms differ in normal healthy subjects (56-57). However, these variations are normal and unlikely to be of significance unless one excursion is at least twice as great as the affected side. In addition, a study assessing the components of the breathing pattern in chronic stroke survivors found increased rib cage contributions during the respiratory cycle in these patients (58). The lower contribution of the abdomen may be related to the decreased diaphragm excursion in the paretic side and also to abdominal muscle weakness. This impaired function of abdominal muscles may affect the synergy between the abdominal and diaphragm muscles, impairing the capacity of the diaphragm to generate force.

The first study that aimed to assess respiratory muscle strength in stroke patients reported a significant decrease in respiratory muscle strength, compared to healthy controls: PI_{max} 53.4 (SD 21.4) and 99.4 (SD 8.4 cmH_2O), respectively; PE_{max} 61.6 (SD 16) and 121.8 (SD 18.1) cmH_2O, respectively (59). More recently, other authors have also reported low values for inspiratory and expiratory muscle strength, ranging from 38.9 to 73.6 cmH_2O for PI_{max} and 50.5 to 89.4 cmH_2O for PE_{max} (58-62).

Chest wall kinematics impairment together with respiratory muscle weakness are the main mechanisms of impaired cough function. Cough is an important mechanism that protects the airways against aspiration, generating high expiratory laminar airflows that dislodge and eject foreign material. A strong and effective cough requires the coordinated activation of respiratory muscles and intrinsecal laryngeal muscles. In a cough manoeuvre, inspiratory muscle contraction causes air to be drawn into the lungs. Expiratory muscle contraction then creates a build-up of intrathoracic pressure against a closed glottis. Finally, a blast of air is released by rapid glottis opening, producing the characteristic cough sound and moving particles from the lungs toward and into the pharynx. Cough function is reduced by one third in stroke patients when compared with healthy matched controls, and uneffective cough has a negative impact on the prognosis of stroke survivors (63-64).

Oropharyngeal dysphagia is defined as abnormal swallowing due to impaired coordination, obstruction, or weakness affecting swallowing biomechanics. It occurs frequently after a stroke event; with an incidence ranging from 19% to 81% (65). This impairment in swallowing efficiency and safety contributes to an increased risk for aspiration and pneumonia. Furthermore, pneumonia risk is more than 3 times greater in stroke patients with dysphagia and 11 times greater in those most severely affected with confirmed aspiration. These findings suggest that dysphagia and aspiration are important predictors for the development of pneumonia (66 - 67).

The clinical definition of pneumonia is based on the presence of a new and persistent infiltrate or consolidation on at least 1 chest X-ray or at least 2 serial chest X-rays in the case of underlying lung disease combined with one of the following clinical signs: fever, leukopenia or leucocytosis and altered mental status in patients older than 70 years, in the absence of other causes. In addition, two of the following signs are required: new onset purulent sputum or change in the character of the sputum, new-onset or worsening cough and worsening gas exchange (68). The term **stroke-associated pneumonia** (SAP) has been used to describe pneumonia that occurs in the first 72 hours of hospital admission. SAP is divided into acute (develops within a month of stroke) and chronic (occurs later than a month) (68). An extensive review concluded that SAP incidence varies between hospitals settings due to high heterogeneity of included studies, especially those performed in critical care units (69). The incidence of pneumonia after a cerebrovascular event ranges from 3.9% to 44% in stroke units and from 3.2% to 11% in rehabilitation units (70-73).

Although several risk factors are associated with SAP development, stroke severity measured by the National Institutes of Health Stroke Scale (NIHSS) or the modified Rankin Scale (mRs) is the major independent risk factor for SAP (74-81). Respiratory muscle dysfunction together with swallowing difficulties and increased aspiration risk are the most frequently identified predictors of post-stroke pneumonia (82). Patients with SAP have higher risk of mortality, longer hospitalizations (3 times longer than those without pneumonia) and require higher levels of care after hospital discharge (83-95).

In summary, stroke patients may present with impaired swallow and respiratory muscle function that affects cough effectiveness and increases the risk of SAP. Thus, an intervention targeting improved respiratory strength and cough effectiveness might reduce the risk of developing post-stroke pneumonia.

- **Lung Cancer**

Lung cancer is a major health problem worldwide, and is histologically divided into two groups: non-small cell lung cancer (NSCLC) representing almost 85% of cases, and small cell lung cancer (SCLC). In NSCLC, lung resection surgery is the best curative option in early stages (I and II) and for appropriately selected patients with locally advanced disease (stage IIIA) (96-97).

Patients undergoing thoracotomy present an increased risk of postoperative pulmonary complications, which is associated with poor clinical outcomes (98-102). Pulmonary complications have been defined as "a pulmonary abnormality that produces identifiable disease or dysfunction that is clinically significant and adversely affects the clinical course" (103). The most frequent postoperative complications are reductions of lung volumes and inefficient cough. As a result, atelectasis in the basal segments and decrease in functional residual capacity may occur, which in turn affects the gas exchange properties of the lung by increasing the ventilation/perfusion mismatch. The situation may be further aggravated by hypoventilation due to sedation, pain and increased mechanical load. The causes of these complications are multifactorial, including respiratory muscle dysfunction induced by the surgical procedure, intraoperative manipulation, anaesthesia, post-operative pain and altered breathing pattern. Furthermore, respiratory muscle weakness may be present before surgery and together with poor preoperative physical functioning and other comorbidities can make patients more vulnerable to postoperative complications (98-102).

Thoracic surgery affects respiratory muscle function by damaging the muscles or changing the mechanics of the respiratory system. To date, several studies have reported the impact of lung resection on respiratory muscle strength. Nomori *et al.* (98) reported a decrease of 50% in PI_{max} at one week after lung resection surgery in patients receiving limited thoracotomy, video-assisted thoracic surgery (VATS) or standard postero-lateral thoracotomy; such reduction on PI_{max} and PE_{max} persisted four weeks after thoracotomy. One point to highlight is that respiratory muscle dysfunction in these patients is not affected by postoperative pain because pain relief by epidural anaesthesia did not reduce diaphragm dysfunction. In this study, older patients (>70 years) had significantly lower values of respiratory muscle strength than younger ones. Furthermore, the risk of pulmonary complications after thoracic surgery was higher in older patients. No significant postoperative differences in PI_{max} and PE_{max} between VATS and limited thoracotomy one week after surgery were observed.

Another study that assessed respiratory muscle strength after lung surgery reported a decrease of 50% on PI_{max} and 40% on PE_{max} two days after postero-lateral thoracotomy; and 24% on PI_{max} and 39% on PE_{max} after transaxillary thoracotomy. No reduction in maximal respiratory pressures was observed after VATS (102). One month after surgery, PI_{max} and PE_{max} values were within normal range. These findings suggest that the type of incision affects diaphragm and chest wall muscle function. Therefore, respiratory muscle strength may be dependent on the type of thoracotomy procedure.

In contrast, another study (104) found no detriments to respiratory muscle strength after the 5th postoperative day. Furthermore, the surgical approach was not associated with PI_{max} values at two weeks after surgery. These differences may be explained by a lesser impairment in respiratory muscle strength following the muscle-sparing technique used in this study.

Patients with lung cancer may have symptoms such as dyspnoea, fatigue, anxiety and pain that contribute to physical inactivity, which usually results in further deconditioning (105-106). In addition to the disease process, cancer treatments (lung resection, adjuvant chemo- or radiotherapy) decrease physical activity and adversely affect respiratory muscle function (107-110). Lung resection surgery is particularly associated with reduced exercise capacity, respiratory muscle dysfunction and impaired quality of life; consequently, the development of strategies targeting enhanced cardiorespiratory fitness and respiratory muscle strength might improve physical functioning and quality of life (111-114).

1.5. Therapeutic approach to respiratory muscle dysfunction

1.5.1. Principles of RMT

The first study applying the principles of strength and endurance muscle training for respiratory muscles was carried out by Leith & Bradley in 1976 (115) and concluded that respiratory muscle strength and endurance might be specifically improved by appropriate training programs.

Threshold loading devices are currently recommended to perform RMT. These devices generally have a spring-loaded valve requiring the patient to inhale strongly enough to open the valve and to breathe in against an individualized load. Optimal training intensity is still unknown, but training loads usually are set to a pressure equivalent to 30% of maximal respiratory pressures and increased as tolerated (116). In the last years, high-intensity interval-based training schedules have been proved to be effective (86 117). Optimal exercise duration is also uncertain; most studies provide a total exercise time of 15-30 min per day with high-intensity protocols (86 117).

The impact of inspiratory muscle training (IMT) in COPD has been extensively studied in the recent years. IMT is shown to be a stand-alone therapy improves inspiratory muscle function (strength and endurance), dyspnoea perception and exercise capacity (116-118). An interesting study demonstrated that IMT increases the proportion of type I fibbers by approximately 38% and size of type II fibbers by approximately 21%, in the external intercostal muscles

(119). The statement of the American Thoracic Society/European Respiratory Society (ATS/ERS) on pulmonary rehabilitation recommends IMT as adjunctive therapy in pulmonary rehabilitation in COPD patients with suspect or proven respiratory muscle weakness defined as PI_{max} <60cmH_2O (120).

In the last five years, RMT has been applied to patients with diseases other than COPD (121-123), but once again there is a wide range of training schedules (type, intensity, duration). Available systematic reviews point to the urgent need of quality studies to determine efficacy and optimal exercise intervention.

1.5.2. Respiratory muscle training in diseases other than chronic obstructive pulmonary disease

- **Inspiratory muscle training in chronic heart failure**

Available studies on IMT in patients with CHF report improvements in many clinical outcomes: dyspnoea, health related quality of life (HRQoL), peripheral muscle and peripheral blood flow, heart rate, Peak VO_2, 6-minute walking distance (6MWD), ventilation, VE/VCO_2 (Minute ventilation - Carbon dioxide production ratio) (121). Different training modalities according to exercise capacity and clinical characteristics have been proposed in a consensus document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation (Figure 8) (24). Some studies have reported that improvements of respiratory muscle strength could be translated to an improvement in functional capacity (125-141).

Patients with CHF with dyspnoea and inspiratory muscle weakness would be the best candidates for IMT. The contraindications appear to be: markedly elevated end-diastolic volume and left ventricular end-diastolic pressure and worsening signs/symptoms of HF after IMT has been initiated.

	Young (<65 years)		**Elderly (≥ 65 years)**	
	Active	**Sedentary**	**Active**	**Sedentary**
VO_{2peak} ≤ 10mL/Kg/min or <300m at 6MWT	CT RT RST LIT	CT RT RST LIT	CT RT RST LIT	CT RT LIT
VO_{2peak} < 10mL/Kg/min to ≤ 18 mL/Kg/min or 300-450 m at 6MWT	CT RT RST IT	CT RT RST	CT RT RST	CT RT
VO_{2peak} > 18 mL/Kg/min or >450m at 6MWT	CT RT* RST HIT	CT RT* RST HIT	CT RT* RST HIT	CT RT* RST HIT

Figure 8. Exercise training prescription in chronic heart failure according to exercise capacity, age and activity habit.

VO_{2peak}: peak oxygen uptake; **6MWT**: 6-minute walking test; **CT:** continuous endurance training; **RT**: respiratory training; **RST**: resistance/strength training; **LIT:** low-intensity interval training; **HIT:** high-intensity interval training.

Adapted from Piepoli et al. Eur J Heart Fail. 2012

IMT method and prescription have been extensively addressed in the literature. The majority of the studies used the pressure threshold type, a relatively inexpensive and easy to administer device, that allows training workload up to 41 cmH_2O (142), whilst other studies used high-intensity devices (125-126,128,141). The trainer device used in the studies of this PhD project was the Orygen dual valve, a portable device that provides workloads up to 70 cmH_2O.

Similarly to COPD, the most prescribed IMT schedule is a training workload of 30-60% of the PI_{max} for 30 min, 5-7 days per week for 4-12 weeks. The greatest gain in respiratory muscle strength is obtained in approximately 4 weeks, after this period, minimal to modest improvements are observed. Similar benefits may be achieved with high-intensity training programs (60-80% of PI_{max}) of a shorter duration that may be more easily included in the clinical practice. Given the negative impact of the disease on muscle system and improvement in patient functioning and HRQoL after IMT (112 143), interventions aiming to improve muscle dysfunction play a role in the management of patients with CHF (143-145).

- ## Respiratory muscle training in stroke

RMT also improves respiratory muscle function in neurological conditions such as: multiple sclerosis and Parkinson’s disease (146-152), but the effects of RMT in stroke patients have not been adequately addressed.

Respiratory muscle weakness is a clinical condition frequently observed in patients after a cerebrovascular accident. It is related to cough impairment, which leads to pulmonary complications and/or lung infections. A meta-analysis (153) revealed that RMT has a small positive effect on inspiratory and expiratory muscle strength in stroke patients: difference of 7 cmH_2O in PI_{max} and 13 cmH_2O in PE_{max} compared with no/sham interventions. Studies included in this review were carried out in patients in the sub-acute phase of rehabilitation, with PI_{max} and PE_{max} of 46 (SD 7) cmH_2O and 59 (SD 6) cmH_2O, respectively. Further studies are required to confirm these findings and determine the clinical impact of RMT in stroke patients.

• Exercise interventions in lung cancer

In the early 2000s, a special interest began to arise in respiratory outcomes in people with lung cancer. Dyspnoea and fatigue are common symptoms that are likely to reduce exercise capacity and result in the adoption of a sedentary lifestyle (96,154-156); HRQoL, functional status and the ability to participate in activities of daily living (ADL) may also be impaired (157-162). In addition, cancer treatment promotes further impairment of exercise capacity and HRQoL (163-164).

Improving exercise capacity is of particular interest in patients with lung cancer, considering the significant prognostic value of VO_{2peak} both pre- and post-surgery (165). Furthermore, lung cancer patients with poor exercise capacity (VO_{2peak} <15 ml/kg/min) are precisely those who benefit most from exercise intervention (166-169). Two trials assessing exercise capacity throughout VO_{2peak} after lung resection surgery have reported increases between 1.1 and 3.5 ml/Kg/min after the exercise intervention (170-171)

Preliminary findings would suggest that exercise intervention (pre- and post-surgery) in the NSCLC population is safe, reduces post-operatory complications and hospital stay, and leads to increased exercise capacity and muscle function, compared with usual care (172). To date, most studies on exercise interventions have focused on aerobic training in continuous models of moderate intensity (60-80% of maximal heart rate or 50-80% of maximum workload) at least three times per week, lasting 4-14 weeks. Resistance training schedules at moderate intensity (i.e., 60-80% one repetition maximum) have also been used. Although there is a wide heterogeneity in exercise programs in published studies, the available evidence shows that the combination of resistance and aerobic training may provide the optimal training program for patients surgically treated for lung cancer (172).

Respiratory muscle weakness contributes to the development of postoperative pulmonary complications (PPC). Therefore, preoperative interventions aimed to strengthen inspiratory muscles may reduce the incidence of PPC. A growing body of evidence shows the impact of preoperative interventions to reduce the risk of complication and improve postoperative outcomes. A systematic review (123) concluded that preoperative IMT improves respiratory muscle function, reducing the risk of pulmonary complications in patients undergoing cardiothoracic surgery. Most of the studies used IMT protocols consisting of training workloads between 15% and 60% of the PI_{max} during 2, and up to 4, weeks, one to three times per day.

Postoperative respiratory physiotherapy combined with incentive spirometry seems not to be effective in reducing PPC after thoracic surgery (173-175). To the best of our knowledge, only one trial has assessed the impact of IMT after lung resection surgery. These authors reported that 2-week IMT did not enhance respiratory muscle strength and had no effect on the frequency of pulmonary complications after lung resection surgery. However, the number of pneumonia and atelectasis cases were higher in the control group than in the intervention group, suggesting that IMT may be effective in preventing PPC (104).

The heterogeneity of RMT programs makes it difficult to conclude which is the optimal training program for patients submitted to lung resection surgery. Therefore, further research is required to determine the best RMT intervention for this particular group of patients.

1.5.3. Nutritional and pharmacological approach

A multidimensional therapeutic approach to muscle dysfunction is required, including exercise interventions, appropriate level of physical activity, and nutritional support. To date, though there have been some positive experiences, no pharmacological treatment has shown clear benefits. One probable reason for the lack of a simple drug treatment is that muscle dysfunction is the consequence of a complex interaction between different general and local factors. The general factors potentially affect all muscle groups, and include nutritional abnormalities, systemic inflammation, oxidative stress, and the effects of tobacco and certain drugs, among others (176).

In advanced stages of chronic diseases, both energy balance and protein balance are disturbed. Therefore, **nutritional therapy** may only be effective if combined with exercise or other anabolic stimuli. The use of **drugs with anabolic, anti-inflammatory and antioxidant properties** can also be helpful in specific populations of patients, especially when muscle dysfunction is associated with the loss of muscle mass (176).

Nutritional supplementation, testosterone and anabolic agents seem to have beneficial effects on muscle mass and strength, quality of life and survival (177-179). Drugs with anti-inflammatory effects should be used with caution, considering their dual effect on the muscles. These drugs can damage and impair contraction, but their use is also associated with muscle growth and regeneration (180-181). Another field that has been explored is the use of nonsteroidal anti-inflammatory agents to modulate muscle structure and function. There is increasing evidence about the beneficial effects of antioxidants such as N-acetylcysteine, vitamin C, vitamin E and α-tocopherol. N-acetylcysteine seems to attenuate low-frequency diaphragm fatigue in healthy humans exposed to resistive breathing (182-185).

Although some reports have described positive effects of dopamine and aminophylline on respiratory muscle contractility, these drugs have never been incorporated into clinical guidelines and settings. A recent study has demonstrated that levosimendan, a calcium sensitizer used in clinical settings to improve myocardium contractility in patients with heart failure, prevents diaphragmatic fatigue induced by loaded breathing in healthy subjects (187). Moreover, levosimendan seems to improve contractility by enhancing the neuromechanical efficiency of the muscle and facilitates the interaction of calcium with troponin C, ameliorating the contractile efficiency of myofilaments. Since levosimendan also acts as a vasodilator, this mechanism might contribute to enhancing oxygen delivery to the muscle, in turn improving its aerobic properties. Finally, it is worth noting that this drug has been shown to improve the strength of fibbers obtained from the diaphragm of patients with COPD (176, 185-188).

2. HYPOTHESIS

Respiratory muscle dysfunction is a prevalent condition in respiratory and non-respiratory diseases. Impaired respiratory muscle function can negatively impact clinical outcomes. Strategies to treat this condition are almost non-existent. Therefore, respiratory muscle training could be a useful therapeutic tool to improve respiratory muscle function in respiratory disorders and other frequent comorbidities.

The specific hypotheses for each of three randomized clinical trials are explained below:

STUDY ≠1: Patients with chronic heart failure would benefit from a high-intensity inspiratory muscle training in improved inspiratory muscle strength, dyspnoea and quality of life.

STUDY ≠2: A specific inspiratory and expiratory muscle training would improve respiratory muscle strength in patients with subacute stroke and might be associated with lower incidence of respiratory complications at 6-month follow-up.

STUDY ≠3: A combined aerobic and resistance training with inspiratory and expiratory muscle training would improve exercise capacity, peripheral and respiratory muscle strength in patients with non-small cell lung cancer submitted to lung resection surgery.

3. OBJECTIVES

STUDY # 1: High-intensity vs. sham inspiratory muscle training in patients with chronic heart failure: a prospective randomized trial. Eur J Heart Fail. 2013 Aug; 15(8):892-901.

Objective: To evaluate the effectiveness, feasibility, and safety of a 4-week high-intensity inspiratory muscle training (hi-IMT) in patients with chronic heart failure.

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STUDY # 2: Inspiratory and expiratory muscle training in subacute stroke: A randomized clinical trial. Neurology. 2015 Aug 18; 85(7):564-72.

Objective 2: To assess the effectiveness, feasibility, and safety of short-term inspiratory and expiratory muscle training (IEMT) in subacute stroke patients

STUDY #3: Combined high-intensity respiratory muscle and aerobic exercise training in patients surgically treated for non-small cell lung cancer: a randomized clinical trial. *In submission*.

Objective 3: To assess the impact of a high-intensity respiratory muscle and aerobic exercise training in patients surgically treated for non-small cell lung cancer (NSCLC).

4. RESULTS

Study # 1: Marco E, Ramírez-Sarmiento AL, Coloma A, **Messaggi-Sartor M,** Comin-Colet J, Vila J, Enjuanes C, Bruguera J, Escalada F, Gea J, Orozco-Levi M. High-intensity vs. sham inspiratory muscle training in patients with chronic heart failure: a prospective randomized trial. Eur J Heart Fail. 2013 Aug; 15(8):892-901.

Study # 2: Messaggi-Sartor M, Guillen-Solà A, Depolo M, Duarte E, Rodríguez DA, Barrera MC, Barreiro E, Escalada F, Orozco-Levi M, Marco E. Inspiratory and expiratory muscle training in subacute stroke: A randomized clinical trial. Neurology. 2015 Aug 18; 85(7):564-72.

Study # 3: Messaggi-Sartor M, Marco E, Martínez-Téllez E, Rodríguez-Fuster A, Palomares C, Chiarella S, Muniesa JM, Orozco-Levi M, Barreiro E, Güell MR. Combined high-intensity respiratory muscle and aerobic exercise training in patients surgically treated for non-small cell lung cancer: a randomized clinical trial. *In submission.*

4.1 Study # 1

Marco E, Ramírez-Sarmiento AL, Coloma A, Sartor M, Comin-Colet J, Vila J, et al. High-intensity vs. sham inspiratory muscle training in patients with chronic heart failure: a prospective randomized trial. Eur J Heart Fail. 2013 Aug;15(8):892–901. DOI: 10.1093/eurjhf/hft035

4.2. Study # 2

Messaggi-Sartor M, Guillen-Solà A, Depolo M, Duarte E, Rodríguez DA, Barrera M-C, et al. Inspiratory and expiratory muscle training in subacute stroke. Neurology. 2015 Aug 18;85(7):564–72. DOI: 10.1212/WNL.0000000000001827

4.3 Study #3

Combined high-intensity respiratory muscle and aerobic exercise training in patients surgically treated for non-small cell lung cancer: a randomized clinical trial.

Messaggi-Sartor M, Marco E, Martínez-Téllez E, Rodríguez-Fuster A, Palomares C, Chiarella S, Muniesa JM, Orozco-Levi M, Barreiro E, Güelll MR.

In submission.

Messaggi-Sartor M, Marco E, Martínez-Téllez E, Rodriguez-Fuster A, Palomares C, Chiarella S, Muniesa JM, Orozco-Levi M, Barreiro E, Güell MR. **Combined high-intensity respiratory muscle and aerobic exercise training in patients surgically treated for non-small cell lung cancer: a randomized clinical trial.** *In submission*.

Title: Combined High-Intensity Respiratory Muscle and Aerobic Exercise Training in Patients Surgically Treated for Non-small Cell Lung Cancer: a Randomized Clinical Trial.

Short title: Respiratory Muscle Training plus Aerobic Exercises for NSCLC Patients.

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This study was registered in clinicaltrials.gov (NCT01771796).

ABSTRACT

Background:

To assess the impact of a combined high-intensity respiratory muscle and aerobic exercise training on patients submitted to lung cancer resection surgery.

Methods:

In a randomized clinical trial, 37 patients with NSCLC eligible for tumor resection assigned to exercise training or usual post-operative care. The 8-week training program consisted of aerobic exercises, peripheral muscle strength exercises and high-intensity respiratory muscle training (24 supervised sessions, 3 per week). Primary outcome was exercise capacity assessed with peak oxygen uptake (VO_{2peak}) during cardiopulmonary exercise test. Secondary outcomes included changes in respiratory and peripheral muscle strength and quality of life assessed with specific and general questionnaires (European Organization for Research and Treatment of Cancer and Short Form 36).

Results:

The 8-week training program was associated with significantly improved peak work rate (Δ15.1, 95%CI 2.7 to 27.5) and maximal inspiratory and expiratory pressures (Δ18.2 [95%CI 5.5 to 30.9], and 12.0 [95%CI 2.2 to 21.7], respectively). No significant differences were observed in VO_{2peak}, peripheral muscle strength and quality of life.

Conclusion:

An 8-week exercise program improved peak work rate and respiratory muscle strength in NSCLC patients after lung resection, but had no impact on health-related quality of life. This study was registered in clinicaltrials.gov (NCT01771796).

Keywords:

Lung cancer, cardiorespiratory fitness, respiratory muscle training, lung resection, quality of life

Introduction

Patients with non-small cell lung cancer (NSCLC) may have symptoms such as dyspnea, fatigue, anxiety and pain that contribute to physical inactivity, which usually results in further deconditioning.[1-2] In addition to the disease process, cancer treatments (lung resection, adjuvant chemo- or radiotherapy) decrease physical activity and adversely affect respiratory muscle function.[3-6] Lung resection surgery is particularly associated with reduced exercise capacity, respiratory muscle dysfunction and impaired quality of life; consequently, the development of strategies targeting enhanced cardiorespiratory fitness and respiratory muscle strength might improve physical functioning and quality of life.[7-10]

A recent meta-analysis concluded that postoperative exercise training improves 6-minute-walking distance and HRQoL in surgical patients with NSCLC stages I-IIIB, many of who underwent adjuvant chemotherapy in addition to lung resection.[11] Most of the interventions consisted of aerobic and resistance exercises; only one included inspiratory muscle training as well. This heterogeneity of participants and interventions makes it difficult to determine the optimal exercise intervention; and even more, there is insufficient evidence to generalize an exercise recommendation for all surgically treated NSCLC patients.

Under the hypothesis that combining aerobic and resistance exercises with inspiratory and expiratory muscle training (IEMT) would improve exercise capacity and peripheral and respiratory muscle strength, the aim of the present clinical trial was to assess the impact of an 8-week exercise intervention in NSCLC patients with functional loss closely related with lung resection.

Material and Methods

A multicentric, prospective, single-blind, randomized controlled trial was designed, according to the Consolidated Standards of Reporting Trials Statements (CONSORT),[12] to determine the effectiveness of a pulmonary rehabilitation program in patients with lung cancer eligible for tumor resection. After receiving information about the study procedures, eligible patients were randomly assigned to the exercise or control groups. Randomization was performed independently by a staff member blinded to patient identity, using a random number generator program. The researchers assessing the main outcomes were blinded to the study group assignments. Outcomes were assessed 1 week before surgery, between 4 and 6 weeks after surgery, and 6 months after surgery. The assessments were performed in the following sequence: maximal respiratory pressures, peripheral muscle strength and cardiopulmonary exercise test. Other data collected were age, sex, anthropometric characteristics, smoking history, comorbidities, cancer type and surgery. The 8-week intervention began at 2 months after lung resection. The clinical trial was approved by the local clinical research ethics committee and performed in accordance with the Declaration of Helsinki. This study was registered in clinicaltrials.gov (NCT01771796). Written informed consent was obtained from all participants.

Patients newly diagnosed with resectable NSCLC were considered for the study. The setting was the pulmonary rehabilitation unit in two tertiary hospitals in the city of Barcelona. Inclusion criteria were age <80 years, diagnosis of stage I or II NSCLC, referral to lung cancer resection by muscle-sparing lateral thoracotomy or videothoracoscopy, and ability to understand and accept the trial procedures. Exclusion criteria included adjuvant treatments such as chemo- or radiotherapy, post-operative complications that would prevent performing a maximal exercise test in the 6 weeks after surgery, previous history of thoracic surgery, and comorbidities adversely interfering with physical performance.

Participants attended their local pulmonary rehabilitation program 3 times per week for 8 weeks. Each session lasted 60 minutes and all exercise training sessions were supervised by a

Respiratory muscle strength, defined as the ability to develop a brief maximal respiratory effort, was assessed through maximal inspiratory and expiratory pressures (PI_{max} and PE_{max}, respectively). PI_{max} was measured at the mouth during a maximum effort from residual volume against an occluded airway; to determine the PEmax, patients performed a maximum expiratory effort from total lung capacity with the occluded airway.[13] The mouthpiece used in the maneuvers had a small orifice to minimize the participation of face and mouth muscles and was connected to a Micro RPM pressure transducer (Micro Medical/Care Fusion, Kent, United Kingdom). A flanged mouthpiece was used to create an optimal mouth seal in the presence of orofacial weakness. The highest value of 3 reproducible maneuvers (10% variability between values) was used for analysis. Reference values were those previously published for a Mediterranean population.[14]

Peripheral muscle strength was estimated for upper and lower limbs with maximal isometric force of hand grip and quadriceps, respectively. Peak handgrip force was assessed with the use of a hand-held dynamometer (Jamar®, Nottinghamshire, UK), with the elbow at 90° flexion, with the underarm and wrist in neutral position.[15] Observed measures were expressed in Kg and as a percentage of the reference values.[16]

Quadriceps force was measured using a hand-held dynamometer (Nicholas Manual Muscle Tester; Lafayette Instrument Company, Lafayette, Indiana, USA), with the patient seated with the hip and knee joints in 90° flexion. The highest val ue of 3 maximum voluntary contractions, defined as the greatest force held for 1 second, was used for analysis.[17-19]

HRQoL was assessed using both specific and generic questionnaires. The European Organization for Research and Treatment of Cancer questionnaire (EORTC QLQ-C30)[20] is an integrated system specifically designed to assess quality of life of cancer patients participating in clinical trials. Single-item measures and scales range in score from 0 to 100. A high score for a functional scale represents ‘a high/healthy level of functioning’ and a high score for the global health status/quality of life represents a ‘high QoL’; however, a high score for a symptom scale/item represents a high level of ‘symptomatology/problems’. The Short Form 36 (SF-36) is a generic, self-administered questionnaire containing 36 items. It measures health on eight multi-item dimensions: physical functioning, role limitations (physical problems), bodily pain, general health, vitality, social functioning, role limitations (emotional problems), and mental health. For each dimension, item scores are coded, summed, and transformed onto a subscale ranging from 0 (worst possible health) to 100 (best possible health). The SF-36 has also been validated for the Spanish population.[21-22]

Sample size was calculated to detect a change in the VO_{2peak} of 2.0 mL/Kg/min and standard deviation (SD) of 2.3 mL/Kg/min, resulting in a required sample of 21 subjects per group to detect significant differences with an alpha-risk of 0.05 and a beta-risk of 20% on a bilateral contrast. The sample size was overestimated to allow potential losses of 10%. Quantitative variables were presented as mean and standard deviation (SD), unless otherwise stated. Univariate analysis was performed using x^2, Fisher exact, Student t-tests, depending on the variables analyzed. Student t-test for independent samples was used for inter-groups analysis and t-test for repeated measures for intra-group analysis. As a measure of intervention effect, the estimated mean difference between groups was reported alongside 95% confidence intervals (95% CI) and p-value. Changes during follow-up were assessed by analysis of variance using a repeated-measures mixed design (intrasubject) and a one-factor (intersubject) design for the analysis of values over time. The level of significance was set at $p \leq 0.05$. Data analysis was performed using the IBM SPSS Statistics v21.

Results

Figure 1 describes the flow of participants through each stage of the study period. A total of 70 patients were screened to participate in the trial. Exclusion from randomization was based on diagnosis other than NSCLC (n= 5), need for chemotherapy or radiotherapy (n= 9), post-operative complications (n= 2), lack of a CPET before surgery (n= 4), refusal to participate (n= 6), and other reasons (n= 7). Finally, 37 patients were randomly assigned to the two study groups, resulting in the allocation of 16 to the exercise intervention and 21 controls. There were 9 dropouts (5 in the intervention group and 4 in the control group), mainly related to transportation issues due to the program's location. Of the remaining 28 patients, 11 were in the exercise group, all of whom completed more than 80% of the training sessions.

Demographic, clinical and functional characteristics of the sample are summarized in Table 1. The mean age was 64.6 (SD 8.5) years and there were 26 (70.3%) men and 11 (29.7%) women. The only significant difference between the groups was a higher proportion of men in the control group. The main outcomes under study were evaluated on an intention-to-treat basis.

Table 1. Demographic and clinical characteristics of participants before exercise intervention.

	Total Sample (n=37)	**Training group (n= 16)**	**Control group (n= 21)**	**p**
Age (years):	64.6 (SD 8.5)	64.2 (SD 8.1)	64.8 (SD 8.9)	>0.05
Sex (%):				
- Men	26 (70.3%)	8 (50.0%)	18 (85.7%)	0.030
- Women	11 (29.7%)	8 (50.0%)	3 (14.3%)	
Body Mass Index (Kg/m^2):	27.2 (SD 3.8)	27.9 (SD 4.7)	26.8 (SD 3.0)	>0.05
Smoking:				
- Current smokers (%)	17 (45.9%)	5 (31.3%)	12 (57.1%)	>0.05
- Never smoked (%)	4 (10.8%)	3 (18.8%)	1 (4.8%)	>0.05
- Past (%)	16 (43.2%)	8 (50.0%)	8 (38.1%)	>0.05
Smoking History (packs/year):	48.0 (SD 20.0)	47.2 (SD 15.0)	50.8 (SD 23.1)	>0.05
Presence of COPD (%):	28 (77.8%)	10 (62.5%)	18 (90.0%)	>0.05
Surgery:				
- Lobectomy (%)	28 (75.7%)	13 (81.3%)	15 (71.5%)	>0.05
- Minor resection (%)	9 (24.3%)	3 (18.8%)	6 (28.6%)	>0.05
Surgery Type:				
- Thoracotomy	35 (94.6%)	15 (93.5%)	20 (95.2%)	>0.05
- Videothoracoscopy	2 (5.4%)	1 (6.5%)	1 (4.8%)	>0.05
Histological Feature:				
- Adenocarcinoma	24 (66.7%)	12 (75.0%)	12 (60.0%)	>0.05
- Squamous cell carcinoma	8 (22.2%)	2(12.5%)	6 (30.0%)	>0.05
- Others	4 (11.1%)	2 (12.5%)	2 (10.0%)	>0.05
Pulmonary Function:				
- FEV_1, % pred	62.7 (SD 16.6)	64.7 (SD 17.1)	58.5 (SD 14.5)	>0.05
- FVC, % pred	82.6 (SD 16.0)	90.0 (SD 5.6)	79.0 (SD 19.0)	>0.05
- FVC/FEV_1, % pred	56.4 (SD 11.7)	59.2 (SD 6.7)	55.0 (SD 14.3)	>0.05
- TLC, % pred	101.0 (SD 13.8)	90.0 (SD 8.5)	108.3 (SD 11.9)	>0.05
- DLCO, % pred	71.6 (SD 12.0)	81.0 (SD 8.5)	65.3 (SD 10.3)	>0.05
Cardiorespiratory Fitness:				
- Peak Oxygen Uptake (mL/Kg/min)	14.5 (SD 2.3)	15.1 (SD 2.3)	14.1 (SD 2.3)	>0.05
- Maximal ventilation (L/min)	42.6 (SD 10.6)	41.8 (SD 12.6)	43.1 (SD 9.0)	>0.05
- Peak work rate (% pred)	71.8 (SD 22.3)	75.0 (SD 22.6)	69.4 (SD 22.4)	>0.05
- Maximal heart rate (% pred)	83.2 (SD 21.3)	84.3 (SD 28.7)	82.3 (SD 13.8)	>0.05
Respiratory Muscle Strength:				
- PImax (cmH_20)	72.8 (SD 28.0)	69.3 (SD 20.0)	75.4 (SD 30.4)	>0.05
- PImax (% pred)	69.0 (SD 26.9)	67.4 (SD 28.2)	70.0 (SD 26.3)	>0.05
- PEmax (cmH_20)	62.9 (SD 17.5)	90.5 (SD 21.8)	105.2 (SD 30.7)	>0.05
- PEmax (% pred)	98.8 (SD 27.9)	62.8 (SD 16.6)	62.9 (SD 18.5)	>0.05
Peripheral Muscle Strength:				
- Handgrip strength (dominant) (% pred)	82.6 (SD 28.8)	74.7 (SD 32.3)	88.6 (SD 24.9)	>0.05
- Handgrip strength (non-dominant) (% pred)	88.1 (SD 28.1)	82.4 (SD 28.4)	92.5 (SD 27.7)	>0.05
- Knee extension (dominant side) (% pred)	76.8 (SD 26.5)	68.2 (SD 20.4)	83.4 (SD 29.1)	>0.05
- Knee extension (non-dominant side) (%pred)	72.1 (SD 22.3)	66.9 (SD 16.9)	76.0 (SD 25.4)	>0.05
Generic Health-Related Quality of Life:				
- SF-36 Physical component*	40.7 (SD 9.8)	36.5 (SD 7.1)	43.1 (SD 10.4)	0.03
- SF-36 Mental component*	43.6 (SD 13.7)	42.9 (SD 11.4)	44.1 (SD 15.1)	>0.05
Quality of LifeEORTC QOL-C30:				
- Global quality of life*	64.6 (SD 20.0)	67.0 (SD 19.1)	62.76 (SD 20.8)	>0.05
- Physical*	94.3 (SD 7.3)	91.5 (SD 8.5)	96.50 (SD 5.4)	>0.05
- Role*	92.6 (SD 12.4)	88.9 (SD 14.9)	96.02 (SD 8.9)	>0.05

- Emotional*	73.0 (SD 24.5)	65.5 (SD 27.2)	78.1 (SD 20.1)	>0.05
- Cognitive*	90.4 (SD 15.0)	85.7 (SD 15.8)	94.4 (SD 13.2)	>0.05
- Social*	79.6 (SD 30.6)	76.6 (SD 28.7)	81.7 (SD 32.4)	>0.05
- Fatigue**	31.1 (SD 20.2)	33.3 (SD 16.2)	29.6 (SD 22.5)	>0.05
- Pain**	26.3 (SD 27.9)	27.7 (SD 29.8)	25.4 (SD 27.1)	>0.05
- Dyspnea **	24.0 (SD 20.4)	24.4 (SD 23.4)	23.7 (SD 18.6)	>0.05

Data are presented as mean and standard deviation (SD) or n (%).

Abbreviations: COPD, chronic obstructive pulmonary disease, defined as FEV1/FVC <70% and FEV_1<80% of predicted value; **FEV_1**, forced expiratory volume in the first second; **%pred,** % of predicted value; **FVC**, forced vital capacity; **PImax**, maximal inspiratory pressure; **PEmax**, maximal expiratory pressure; **SF-36:** Short Form 36; **EORTC QOL-C30,** European Organization for Research and Treatment of Cancer (EORTC) Quality of Life.

* Higher scores indicate better functioning (scaled from 0-100).
** Lower scores indicate fewer symptoms (scaled from 0-100).

Lung resection surgery led to significant reductions in exercise capacity (from 17.2 to 14.5 ml/Kg/min, [95% CI -3.79 to -1.7]), peak work rate (from 93.2 to 86.0 watts, 95%CI -15.7 to 1.37), and $\%PE_{max}$ (from 71.3 to 62.8, 95%CI 1.2 to 15.7). No significant decreases in peripheral muscle strength were observed.

Table 2 shows intergroup differences between baseline and post-intervention. The 8-week exercise program was associated with significant improvement in peak work rate predicted values (15.1 [95% CI 2.7 to 27.5]) and maximal respiratory pressures (18.2 [95%CI 5.5 to 30.9] for $\%PI_{max}$ and 12.0 [95%CI 2.2 to 21.7) for $\%PE_{max}$). No significant training effect was observed for exercise capacity and peripheral muscle strength.

Table 2. Intergroup differences between baseline and post-intervention follow-up: respiratory and peripheral muscle strength, cardiorespiratory fitness parameters and pulmonary function.

	Before intervention		**After intervention**			
	Training Group (n=11)	Control Group (n=17)	Training Group (n=11)	Control Group (n=17)	Between-Group Difference Difference (95%CI)	p-value
Peak Oxygen Uptake (ml/min/Kg)	15.2 (SD 1.85)	13.9 (SD 2.12)	16.6 (SD 2.20)	14.2 (SD 2.66)	1.03 (-1.06 to 3.12)	0.320
Maximal Heart Rate (beats/min)	123.1 (SD 18.3)	121.2 (SD 18.8)	130.6 (SD 22.5)	120.7 (SD 15.8)	7.9 (-2.5 to 18.4)	0.129
Peak Ventilation, L/min	43.1 (SD 12.1)	40.8 (SD 7.8)	49.5 (SD 10.7)	40.9 (SD 10.4)	6.2 (- 0.7 to 13.1)	0.077
Peak Work Rate (% pred)	80.1 (SD 21.9)	68.3 (SD 24.4)	99.7 (SD 33.4)	72.8 (SD 23.9)	15.1 (2.7 to 27.5)	**0.019**
Maximal inspiratory pressure (%)	71.6 (SD 32.9)	68.2 (SD 26.1)	94.2 (SD 39.3)	72.7 (SD 27.2)	18.2 (5.5 to 30.9)	**0.007**
Maximal expiratory pressure (%)	64.3 (SD 19.6)	62.8 (SD 19.3)	84.8 (SD 24.0)	71.4 (SD 19.4)	12.0 (2.2 to 21.7)	**0.018**
Handgrip Strength Dom, %pred	81.4 (SD 36.8)	89.5 (SD 25.3)	88.9 (SD 31.0)	92.7 (SD25.1)	4.22 (- 6.1 to 14.6)	0.410
Handgrip Strength NDom, %pred	88.2 (SD 31.3)	92.2 (SD 22.4)	87.9 (SD 31.8)	93.4 (SD 22.8)	-1.4 (-16.1 to 13.1)	0.836
Quadriceps Strength Dom, %pred	61.8 (SD 11.4)	85.5 (SD 30.2)	65.1 (SD 14.7)	82.2 (SD 36.5)	6.5 (-13.5 to 26.5)	0.511
Quadriceps Strength NDom, %pred	61.6 (SD 9.0)	80.1 (SD 25.9)	64.5 (SD 18.7)	78.4 (SD 32.3)	4.6 (-11.7 to 20.8)	0.567

Abbreviations: 95%CI, 95% confidence interval; **%pred**, % of predicted value; **Dom**, dominant; **NDom**, no dominant; **FEV_1**, forced expiratory volume in the first second. **Dom**, dominant side; **NDom,** non-dominant side.

Table 3 shows HRQoL before the exercise intervention and at 6 months after surgery (after exercise intervention). After lung resection previous to the exercise intervention, patients reported a worsening of physical functioning, emotional role and symptoms like fatigue, pain and dyspnea. At 6 months, both groups improved on most of the scores of the HRQoL questionnaires; however, no significant differences between groups were observed.

Table 3. Changes in health-related quality of life assessed with the Short Form 36 (SF-36) and the European Organization for Research and Treatment of Cancer Quality of Life (EORTCQL-30) questionnaires.

	Before Surgery		Before Exercise Intervention		After Exercise Intervention		
	Training Group (n= 11)	**Control Group (n= 17)**	**Training group (n= 11)**	**Control group (n= 17)**	**Training Group (n=11)**	**Control Group (n=17)**	**P-value**
SHORT FORM 36							
Physical Function	42.3 (SD 11.8)	48.6 (SD 5.7)	37.7 (SD 8.3)	40.7 (SD 11.4)	42.9 (SD 7.1)	43.7 (SD 11.9)	0.23
Physical Role	43.2 (SD 10.4)	50.7 (SD 9.0)	33.9 (SD 9.0)	39.3 (SD 9.2)	39.2 (SD 10.3)	42.8 (SD 13.2)	0.37
Body Pain	48.6 (SD 12.5)	50.5 (SD 12.5)	39.7 (SD 11.0)	36.8 (SD 11.9)	42.1 (SD 9.5)	47.3 (SD 9.6)	0.51
General Health	43.4 (SD 9.6)	43.2 (SD 7.5)	43.2 (SD 8.7)	45.9 (SD 9.2)	40.3 (SD 8.5)	45.4 (SD 10.6)	0.28
Vitality	46.1 (SD 10.7)	55.0 (SD 8.1)	46.4 (SD 9.0)	48.9 (SD 12.9)	46.6 (SD 10.0)	53.5 (SD 13.1)	0.25
Social Function	43.9 (SD 11.2)	47.3 (SD 13.7)	38.9 (SD 12.7)	42.6 (SD 12.3)	38.5 (SD 12.2)	51.7 (SD 8.1)	**0.01**
Emotional Role	46.3 (SD 8.9)	49.1 (SD 7.9)	41.5 (SD 14.5)	45.8 (SD 9.2)	42.4 (SD 10.4)	45.1 (SD 13.5)	0.43
Mental Health	40.7 (SD 13.2)	45.5 (SD 14.2)	43.8 (SD 12.3)	41.7 (SD 15.4)	40.5 (SD 11.2)	50.0 (SD 14.1)	0.39
PCS	45.1 (SD 10.0)	50.6 (SD 6.8)	36.8 (SD 10.0)	42.0 (SD 10.5)	41.2 (SD 9.7)	45.6 (SD 9.4)	0.80
MCS	44.6 (SD 9.8)	48.4 (SD 10.1)	46.3 (SD 13.9)	45.6 (SD 11.6)	42.1 (SD 13.4)	51.2 (SD 13.2)	0.28
EORTCQL-30							
Global Quality of Life	68.1 (SD 24.3)	79.7 (SD 23.2)	62.1 (SD 23.3)	66.1 (SD 20.2)	64.4 (SD 24.1)	76.2 (SD19.8)	0.998
Physical	96.4 (SD 8.6)	98.2 (SD 3.9)	94.5 (SD 7.1)	95.6 (SD 6.0)	87.2 (SD 29.4)	93.8 (SD 8.5)	0.474
Role	95.4 (SD 10.7)	91.1 (SD 26.6)	89.4 (SD 15.3)	94.4 (SD 10.2)	86.3 (SD 29.6)	96.6 (SD 9.3)	0.743
Emotional	73.4 (SD 24.6)	83.5 (SD 22.1)	68.9 (SD 25.2)	76.6 (SD 20.2)	69.5 (SD 32.5)	77.2 (SD 26.0)	0.825
Social	89.4 (SD 17.1)	100.0 (SD 0.0)	78.7 (SD 29.8)	82.1 (SD 31.0)	77.2 (SD 30.0)	86.9 (SD 25.4)	0.317
Cognitive	90.0 (SD 14.0)	95.5 (SD 7.6)	89.9 (SD 11.6)	92.2 (SD 15.2)	81.6 (SD 31.8)	83.3 (SD 30.8)	0.868
Fatigue	20.1 (SD 16.3)	4.4 (SD 7.0)	32.3 (SD 17.5)	31.8 (SD 24.8)	26.2 (SD 18.1)	25.9 (SD 25.4)	0.163
Nauseas/Vomiting	4.5 (SD 10.7)	0.0 (SD 0.0)	1.5 (SD 5.0)	0.0 (SD 0.0)	1.5 (SD 5.0)	5.5 (SD 12.0)	0.608
Pain	13.2 (SD 17.1)	10.0 (SD 18.7)	19.9 (SD 27.0)	30.0 (SD 30.3)	15.0 (SD 26.5)	18.9 (SD 16.5)	0.498
Dyspnea	14.8 (SD 17.5)	4.4 (SD 11.7)	29.6 (SD 26.1)	28.8 (SD 17.2)	11.1 (SD 16.7)	11.1 (SD 16.2)	0.622
Insomnia	9.1 (SD 15.5)	11.1 (SD 24.1)	33.3 (SD 29.8)	31.1 (SD 32.1)	27.2 (SD 35.9)	31.1 (SD 42.6)	0.917
Appetite Loss	6.6 (SD 14.0)	0.0 (SD 0.0)	23.3 (SD 27.4)	14.2 (SD 31.2)	0.0 (SD 0.0)	4.7 (SD 17.8)	0.536
Constipation	24.2 (SD 33.6)	8.8 (SD 26.6)	27.2 (SD 41.6)	15.5 (SD 35.3)	3.0 (SD 10.0)	13.3 (SD 21.1)	0.036
Diarrhea	12.1 (SD 16.8)	4.4 (SD 11.7)	9.1 (SD 21.5)	6.6 (SD 25.8)	3.0 (SD 10.0)	11.1 (SD 16.2)	**0.058**
Financial Difficulties	9.1 (SD 21.5)	2.3 (SD 8.8)	9.1 (SD 30.1)	11.9 (SD 28.0)	0.0 (SD 0.0)	7.1 (SD 19.3)	0.09

Abbreviations: PCS, physical component summary; MCS, mental component summary.

Discussion

An 8-week exercise program consisting of aerobic exercise and high-intensity IEMT designed for patients with resectable NSCLC leads to significantly increased peak work rate and respiratory muscle strength at 6 months after lung resection.

Cardiopulmonary exercise testing (CPET) is a unique tool to assess the mechanisms of exercise tolerance.[23] As suggested by other authors, patients in the intervention group achieved higher workloads: %peak work rate difference of 15.1 (95%CI 2.7 to 27.5). Poor exercise capacity (defined as VO_{2peak} <15ml/kg/min) has been shown to be a major determinant of post-operative morbidity and mortality following lung resection surgery.[24-25] Although at 6-month follow-up, there were no between-group differences in VO_{2peak}: 1.03 (95%CI -1.06 to 3.2), patients in the intervention group surpassed the threshold of 12-15ml/Kg/min for VO_{2peak}[26]; patients in the control group did not. Some authors have suggested that a 10% increase in VO_{2peak} is clinically relevant in severely deconditioned patients after lung resection.[27] An increase of almost 10% in VO_{2peak} was observed in the exercise group, compared to 5.7% in the control group. To our knowledge, the only two studies[28-29] assessing exercise capacity throughout VO_{2peak} after lung resection surgery reported increases between 1.1 and 3.5 ml/Kg/min after an exercise intervention, compared to 1.4 ml/Kg/min in the present study. The discrepancies between these three studies may be due to differences in the intensity, length, and modality of the training programs. The successful VO_{2peak} increase reported by Edvardsen E *et al.*[29] also could be associated with better cardiorespiratory fitness at baseline: 19.2 ml/Kg/min versus 15.2 ml/Kg/min in our study. In addition, 80% of our sample were COPD patients, compared to 52% in their study.

The impact of respiratory muscle training after lung resection has not been fully addressed in the medical literature. Our study showed a significant increase in respiratory muscle strength following high-intensity IEMT. An earlier study showed that

2 weeks of inspiratory muscle training at a target intensity of 30% of PI_{max} had no effect on respiratory muscle strength after lung resection surgery.[30] The reason for this difference is likely related to training intensities; higher workloads are expected to induce a high training effect in a shorter time, which might be an advantage for improving rehabilitation efficiency. A highlight of our study was that high-intensity IEMT was well tolerated and no adverse effects were observed.

Lung resection leads to impairments in HRQoL and to psychological distress, such as the feelings of anxiety and depression often observed in cancer patients.[31-32] In addition, NSCLC patients present with lower scores in the mental domains of the HRQoL questionnaire, compared to people with other cancer types or the general population, and also tend to adopt a more sedentary activity level.[33-35] There is some evidence that exercise interventions improve HRQoL in cancer patients.[36] To date, however, there are conflicting results concerning the impact of exercise intervention after lung resection surgery. The majority of studies show no change in HRQoL after an exercise intervention.[36] Nevertheless, these studies assessed HRQoL using only generic questionnaires, which could have influenced the results. In our study, no changes were observed with the use of a more specific questionnaire commonly used in Oncology (EORTC QLQ-C30); unfortunately, however, the disease-specific modules for lung cancer (LC13 or LC17) were not available to us. Therefore, we cannot draw any conclusions about the difference between generic and disease-specific questionnaires. Further studies using specific modules of the EORTC QLQ-C30 modules are needed to investigate the HRQoL effects of an exercise intervention after lung resection for NSCLC.

This study have several limitations. First, the attrition rate was higher than expected. At least 21 patients in each group was the required sample size to detect changes in VO_{2peak} of 2.0 (SD 2.3) mL/Kg/min, but 31% of the intervention group was lost to follow-up. Second, no specific dyspnea scale was included as an outcome variable in the study design; some studies have reported improvements in dyspnea perception after IEMT.[38,-39] Other variables also could have been considered, such as distance walked in a 6-minute test, respiratory complications or nutritional status. Another limitation that could partially explain the limited improvement in exercise capacity is the training protocol (training workload of 60-70% of the peak workload achieved on the CPET, 3 sessions per week during 8 weeks). A 20-week treadmill intervention at 80-90% of maximal heart rate resulted in higher improvements in VO_{2peak} in lung cancer patients after surgery.[29] Our intervention was performed in two different hospitals by different physiotherapists, which might also have influenced the results. Finally, assessments were performed 2 months after completing the training program; a greater improvement would have been likely if evaluated immediately upon completion of the training.

In conclusion, exercise intervention plus high-intensity IEMT leads to improvements in peak exercise workload achieved in the CPET and respiratory muscle strength by NSCLC patients with functional decline secondary to lung resection. The absence of improvement in HRQoL raises questions about recommending an 8-week exercise program, to all patients after lung resection. The effects of this intervention in patients with advanced stages requiring chemotherapy should be assessed in further studies to determine the optimal exercise intervention for each group of patients.

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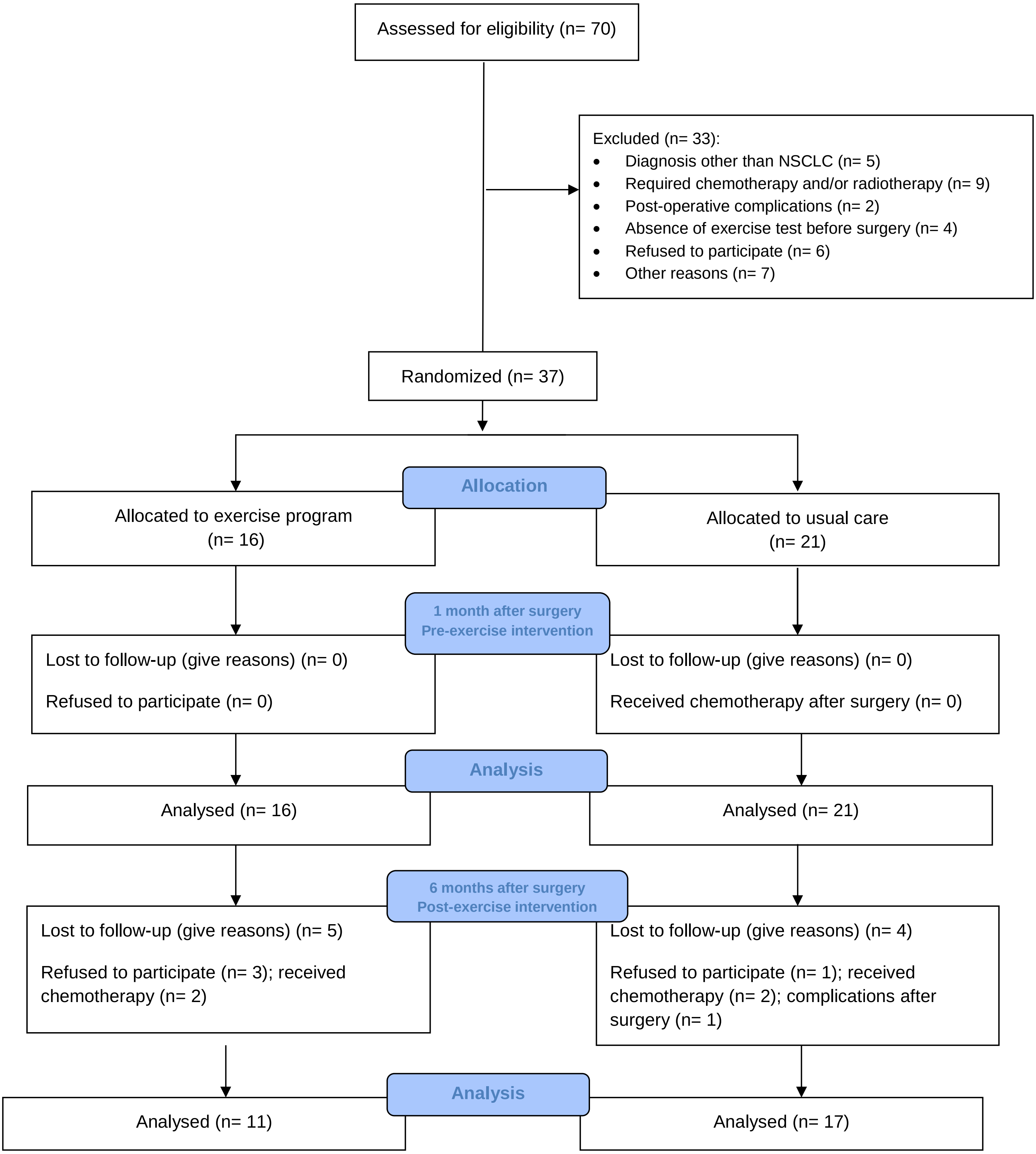
Figure 1. CONSORT 2010 Flow diagram



DISCUSSION

Many chronic diseases lead to impaired function of both peripheral and respiratory muscles, influencing a patient's performance of activities of daily living and quality of life. The three studies included in this research aimed to contribute knowledge about new therapeutic approaches to the management and treatment of respiratory muscle dysfunction in respiratory diseases other than COPD, and also in non-respiratory diseases such as CHF and stroke.

Available evidence indicates that RMT may be an effective treatment modality in patients with COPD and CHF to improve respiratory muscle strength and endurance, resulting in reduction of dyspnoea and improvement in functional capacity and HRQoL, especially when considering RMT in addition to general exercise training. There are still many questions to be answered: what patients may benefit more from RMT? Should both inspiratory and expiratory muscles be trained? Should we train the strength or endurance of the respiratory muscles? In which cases and at which intensity level?

Chronic heart failure

Patients with CHF exhibit significantly reduced strength and endurance of the respiratory muscles, which is related to reductions in exercise capacity and inefficient ventilation (189-192). IMT has emerged as an effective therapeutic tool to improve many clinical outcomes in CHF, including dyspnoea, HRQoL, peripheral muscle blood flow, peak VO_2, 6MWD and oxygen uptake efficiency (34, 40, 125-132, 134-136, 138-140, 193,194). There are some gaps in the evidence about the appropriate prescription of IMT that need to be elucidated.

First, there is no consensus about the optimal training schedule. Both low-intensity (30% to 60% of the PImax) and high-intensity training protocols (<60% of the PImax) have shown significantly improved clinical outcomes in patients with CHF (34, 40, 125-132,134-136,138-140,193,194). Given that most of the studies using high-intensity protocols have been performed in samples with preserved respiratory muscle function, the impact of high-intensity protocols in CHF patients with inspiratory muscle weakness should also be studied. Although it is possible to assume that CHF patients cannot support high workloads, patients in our study who performed a high-intensity protocol reported good tolerance and acceptance and there were no adverse events.

Second, the reduced inspiratory muscle endurance reported in previous studies (191,195) is unexpected in patients with CHF. The diminished inspiratory/expiratory flow and excessive VE for a given level of CO_2 in these patients might be the key factors compromising inspiratory muscle endurance (134, 190-192, 196-198). In the diaphragm of patients with CHF there is a shift from a fast to slow myosin-heavy chain, increasing oxidative capacity and decreasing glycolytic capacity, which contrasts with the histochemical changes observed in the limb muscles of these patients (199). These findings suggest that endurance muscle training could play an important role in patients with CHF. The assessment of functional properties of respiratory muscles is mandatory for a correct prescription of a training protocol. High-intensity IMT (60%-80% of the PI_{max}) is expected to induce greater changes in strength, compared to low-intensity IMT, and is more likely to facilitate endurance gains.

Third, IMT attenuates the metaboloreflex mechanism in the inspiratory muscles, improves limb blood flow under inspiratory loading and results in better exercise performance in patients with CHF (40). Moreover, in combination with aerobic exercise, IMT results in greater changes in exercise capacity than aerobic training alone (131, 200). In view of these findings, combined protocols could have a synergistic positive effect in patients with CHF.

Although the Heart Failure Guidelines of the European Society of Cardiology firmly recommend regular physical activity and structured exercise training, cardiac rehabilitation programs are still poorly implemented in the clinical practice (201). The Statement on Exercise Training in Heart Failure of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation is a general guide to proposed indications for the prescription of training modalities. It also provides practical advice for the application of exercise in heart failure and how to overcome traditional barriers, based on the current scientific and clinical knowledge supporting the beneficial effect of this intervention (124).

Stroke

The impairment of respiratory muscle function after a strol 105 related to the disruption of central motor output, as opposed to intrinsic loss of peripheral muscle strength (61). This impairment is associated with deconditioning, functional limitations, and respiratory complications (202). Some evidence suggests that respiratory muscle weakness may underlie significant impairments

in cough function, contributing to chest infections and death 107 201). An effective cough requires a strong expiratory effort and rapid expiratory airflow, among other factors (203). A systematic review of the effects of RMT (inspiratory and/or expiratory) after stroke found that it increases respiratory muscle strength in very weak individuals after stroke and reduces their risk of respiratory complications (153). Considering clinical impairments induced by stroke and the beneficial effects of RMT, it is possible to think that improving expiratory muscle strength is particularly important in these patients. Moreover, specific EMT effectively improves cough function in healthy subjects and in some neurological disorders (204-205). Although current evidence is insufficient to recommend the use of RMT to improve cough and swallowing function in patients after stroke, implementing interventions aimed to prevent the occurrence of respiratory complications may substantially improve long-term patient outcomes.

Lung Cancer

Lung cancer patients often become deconditioned, with skeletal muscle weakness and exercise intolerance. Cancer treatment is associated with significant morbidity, functional limitations and decreased quality of life. In addition to the foregoing, patients submitted to cardiothoracic surgery are more likely to develop respiratory complications.

The functional management of lung cancer patients has two major targets: to improve exercise capacity and reduce the occurrence of post-operative complications. A comprehensive assessment of patients before undergoing lung resection would help to determine the focus of the exercise intervention -pre-surgical, post-surgical or both- and establish the optimal modality, intensity and frequency. Some studies have suggested that pre-surgical interventions 108
improve exercise capacity, reduce postoperative complications, and shorten length of stay, while post-surgical interventions are more likely to improve functional capacity and quality of life (172). A systematic review illustrates the infancy of our knowledge about the benefits of exercise interventions in lung cancer (172). Most of the studies included in the review were observational and investigated a wide range of outcomes, resulting in a disparate set of data for systematic analysis. Randomized clinical trials about the impact of exercise interventions before and after surgery are needed. Moreover, it is necessary to establish the most desired outcomes to be evaluated and the appropriate measurement methods to be used.

The effects of RMT to improve exercise capacity in lung cancer patients remain unknown. At present, its use is aimed to prevent post-surgical complications. Preoperative IMT for at least 2 weeks leads to significant improvements in respiratory muscle strength following cardiothoracic or upper-abdominal surgery, significantly reducing the risk of post-operative complications (123). Considering the negative impact of lung resection surgery on respiratory muscles, IMT interventions before surgery could play an important role in reducing the occurrence of respiratory complications. The rationale of maintaining strong respiratory muscles is that inspiratory muscles assist post-operative lung expansion and expiratory muscles are important for secretion clearance, preventing atelectasis and pneumonia. Dual training protocols focused on improving the strength of inspiratory and expiratory muscles in order to reduce post-surgical complications might be of special interest in this group of patients.

Despite the benefits of aerobic training to improve exercise capacity in patients submitted to lung resection (171, 172), then timeframe between diagnosis of lung cancer and surgery is usually limited. For this reason, aerobic exercise could be indicated in very deconditioned patients pre-surgery and in patients with functional loss post-surgery.

Cancer care is currently being directed toward the development of strategies to improve overall functioning and longevity. At present, exercise interventions for patients submitted to lung resection surgery are inadequately implemented in clinical practice. A particular effort should be made to develop “prehabilitation programs” to help patients to arrive to surgery in optimal condition.

In summary, a universal agreement on exercise prescription for patients with CHF, stroke and lung cancer does not exist. Therefore, an individualized approach is recommended. Careful clinical and functional evaluation is the key point in the optimal rehabilitation of patients with muscle dysfunction, regardless of its aetiology.

6. CONCLUSIONS

Three major conclusions emerged from this research project:

- CHF promotes significant impairment in the structure and function of the respiratory muscles. The use of IMT leads to changes in strength and endurance that result in improvements in dyspnoea perception, and exercise and functional capacity in patients with CHF.

- IEMT appears to be a useful tool to improve respiratory muscle strength during post-acute stroke rehabilitation. Fewer respiratory complications at 6 months in the intervention group suggest that IEMT could be considered for inclusion in stroke rehabilitation programs.

- Exercise intervention added to high-intensity IEMT leads to improvements in respiratory muscle strength and in peak exercise workload achieved in CPET by NSCLC patients with functional decline secondary to lung resection. The absence of improvement in HRQoL raises questions about recommending an 8-week exercise program to all patients after lung resection.

7. FUTURE DIRECTIONS

There are good reasons to believe that the next years will bring increased knowledge about muscle dysfunction and new therapeutic approaches to the management of a wide variety of diseases (CHF, stroke and lung cancer, among others) including an expanded use of rehabilitation programs. Although rehabilitation is indicated in patients with chronic respiratory diseases and CHF, the use of comprehensive rehabilitation programs is still relatively limited. Rehabilitation has a considerable effect, not only on muscle function, but also on the reduction of complications and improved exercise tolerance, quality of life and survival. It is important to note that not all patients will respond to muscle training, especially in the most advanced stages of disease when nutritional disorders become relevant.

The management of muscle dysfunction associated to critical acute illness has emerged as an interesting field of research in the recent years. Peripheral skeletal muscle wasting and weakness during the period of mechanical ventilation and immobilization associated with intensive care unit (ICU) admission are considered significant drivers underlying much of the impairment in physical function. This functional loss may persist long after ICU discharge. Rehabilitation strategies are once again the cornerstone of managing morbidity related to critical illness. Early mobility in the ICU results in significant functional improvement; however, the impact of these interventions after ICU discharge are not clear. The development of robust tools to measure response to therapeutic options is required. Moreover, future trials evaluating rehabilitation effectiveness must employ measures to accurately capture response to therapy.

The impact of RMT in patients with stroke deserves a special mention. Some evidences suggest that RMT can be considered a feasible intervention to be implemented in clinical practice. To date, the influence of respiratory muscle dysfunction on the presence of respiratory complications (pneumonia and lung infections) is not well established. Well-designed studies to assess the impact of RMT on clinical outcomes such as lung infections and mortality are required, especially in stroke patients with dysphagia in the chronic stages of the disease.

There is strong evidence supporting the use of rehabilitation programs in the clinical management of patients with chronic diseases. Rehabilitation therapies are usually delivered both in hospital and on an outpatient basis, but accessibility and adherence remain limited and the benefits tend to wane gradually over time. Telerehabilitation, the use of telecommunications technologies in rehabilitation services, is a promising new approach to improve accessibility and adherence to rehabilitation programs.

Further research should be focused on the identification of patients who most can benefit from exercise interventions including RMT, the development of training protocols to optimize clinical outcomes, and implementation of rehabilitation programs to be applied to larger populations of patients, particularly the role of Telerehabilitation to improve patient adherence to rehabilitation programs.

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