Citation: Manifield, James Richard (2022) Effects of inspiratory muscle training in older adults. Doctoral thesis, Northumbria University.

EFFECTS OF INSPIRATORY MUSCLE TRAINING IN OLDER ADULTS

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PhD

2022

EFFECTS OF INSPIRATORY MUSCLE TRAINING IN OLDER ADULTS

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A thesis submitted in partial fulfilment of the
requirements of the University of Northumbria
for the degree of Doctor of Philosophy

Research undertaken in the Faculty of Health
& Life Sciences, Department of Sport,
Exercise, and Rehabilitation

May 2022

ABSTRACT

Background: Respiratory muscle strength is reduced during the healthy ageing process, which can contribute to impaired exercise tolerance in older adults. Inspiratory muscle training (IMT) may improve respiratory muscle strength and thus exercise capacity in this population. Whether IMT is associated with changes in the action of the respiratory muscles during exercise currently remains unknown. Technological advances allow breath-by-breath assessment of compartmental thoracoabdominal volumes during exercise via optoelectronic plethysmography (OEP). Changes in the volumes of the rib cage (RC) compartment represent the action of the intercostal muscles and the diaphragm, whereas abdominal volume changes are reflected by the action of the muscles of the abdominal wall.

Objectives: 1) To perform a systematic review and meta-analysis on IMT in healthy older adults, 2) to determine the age-related differences in acute thoracoabdominal volume responses during inspiratory muscle loading at low, medium, and high intensities, 3) to determine whether an 8-week IMT programme improves respiratory muscle strength, exercise capacity, and the relative contribution of the different respiratory muscle group to tidal volume (V_T) expansion during sub-maximal exercise, and 4) to explore older adults' perspectives and views towards the IMT both immediately following IMT and at 3-months post-IMT.

Methods: OEP was employed to assess thoracoabdominal volume regulation during tapered flow resistive loading (TFRL) acutely but also before and after 8 weeks of IMT (30 breaths, twice daily, at 50% maximal inspiratory pressure; PI_{max}) or SHAM-IMT (30 breaths, twice daily, at 10–15% PI_{max}) in healthy older adults. Interviews were conducted in a subgroup of participants following the training programme.

Results: The meta-analysis found that IMT significantly improves inspiratory muscle strength, reflected by an increase in PI_{max} of 24.7±22 cmH_2O, and results in a non-significant, albeit minimum clinically important difference (MCID), in six-minute walk distance (6MWD) equivalent to 24.7±22.1 m in older adults. During acute application of TFRL at high intensities (50% and 70% PI_{max}) older adults exhibited significantly lower RC V_T expansion compared to their younger counterparts suggesting reduced intercostal muscle activation.

Following an 8-week IMT intervention, PI_{max} was significantly increased by 20.0±11.9 cmH_2O in older adults within the experimental group (p=0.001), which was not the case in the control (SHAM-IMT) group (by 2.4±9.3 cmH_2O; p=1.000). Breathing discomfort was significantly reduced following IMT during a bout of training at 50% PI_{max} (from Borg scale ratings of 3.5±0.9 to 1.7±0.8). Furthermore, IMT-induced significant improvements in the 6MWD in the experimental group (by 18.8 ± 28.4 m; p=0.042) with no change in the SHAM-IMT group (change of −0.5 m; p=0.956). During constant work rate (CWR) cycling reproducing external work rate and minute ventilation ($\dot{V}_E$) pre- to post-IMT, the change in volume of the RC compartment was significantly associated with the change in total V_T in the IMT group (r=0.781, p=0.008) but not the SHAM-IMT group (r=0.119, p=0.727), suggesting concurrent training adaptations of the intercostal muscles and the diaphragm.

The majority of participants reported positive experiences with IMT, and facilitators to training were identified including that the device was easy to use and the sessions were not time-consuming. Improved perceived exercise capacity and reduced sensations of breathlessness were reported by some participants, with those not perceiving any changes post-IMT attributing the lack of effect to having high baseline physical activity levels.

Conclusions: The findings from this thesis support previous literature in that IMT can significantly improve respiratory muscle strength and exercise capacity in healthy older adults. Furthermore, this work has expanded our current knowledge in this area by exploring IMT-induced physiological changes in respiratory muscle kinematics during exercise, along with providing qualitative evidence that IMT is well-tolerated in this population.

PUBLICATIONS & CONFERENCE PROCEEDINGS

Peer-reviewed publications arising from this thesis

Manifield, J., Winnard, A., Hume, E., Armstrong, M., Baker, K., Adams, N., ... & Barry, G. (2021). Inspiratory muscle training for improving inspiratory muscle strength and functional capacity in older adults: a systematic review and meta-analysis. *Age and ageing*, *50*(3), 716-724.

Manifield, J., Chynkiamis, N., Alexiou, C., Megaritis, D., Hume, E., Barry, G., & Vogiatzis, I. (2021). Acute thoracoabdominal and hemodynamic responses to tapered flow resistive loading in healthy adults. *Respiratory Physiology & Neurobiology*, *286*, 103617.

Conference proceedings arising from this thesis

British Thoracic Society winter conference 2020

Manifield, J., Chynkiamis, N., Alexiou, C., Megaritis, D., Hume, E., Barry, G., & Vogiatzis, I. (2021). P245 Acute thoracoabdominal and central haemodynamic responses to inspiratory muscle loading in healthy young adults.

Manifield, J., Winnard, A., Hume, E., Armstrong, M., Baker, K., Adams, N., ... & Barry, G. (2021). P79 Inspiratory muscle training for improving inspiratory muscle strength and functional capacity in older adults: a systematic review and meta-analysis.

Other publications and conference proceedings arising alongside this thesis

Chynkiamis, N., Armstrong, M., **Manifield, J.**, Hume, E., Reilly, C., Aliverti, A., ... & Vogiatzis, I. (2019). Hemodynamic effects of portable non-invasive ventilation in healthy men. *Respiratory Physiology & Neurobiology*, *268*, 103248.

Hume, E., Ward, L., Wilkinson, M., **Manifield, J.**, Clark, S., & Vogiatzis, I. (2020). Exercise training for lung transplant candidates and recipients: a systematic review. *European Respiratory Review*, *29*(158).

Hume, E., Armstrong, M., **Manifield, J.**, McNeillie, L., Chambers, F., Wakenshaw, L., ... & Vogiatzis, I. (2020). Impact of COVID-19 shielding on physical activity and quality of life in patients with COPD. *Breathe*, *16*(3).

Chynkiamis, N., Lane, N. D., Megaritis, D., **Manifield, J.**, Loizou, I., Alexiou, C., ... & Vogiatzis, I. (2021). Effect of portable noninvasive ventilation on thoracoabdominal volumes in recovery from intermittent exercise in patients with COPD. *Journal of Applied Physiology*, *131*(1), 401-413.

Naples, R., **Manifield, J.**, Chynkiamis, N., Brodlie, M., Brodlie, M., Fenton, A. C., ... & O'Brien, C. J. (2021). Use of Optoelectronic Plethysmography to Assess the Ventilatory Response to Exercise in School-Aged Children Born Preterm. In *Pediatric Pulmonology, 56,* S85-S85.

Chynkiamis, N., Megaritis, D., **Manifield, J.**, Loizou, I., Alexiou, C., LoMauro, A., ... & Vogiatzis, I. (2021). S13 Effect of portable non-invasive ventilation on thoracoabdominal volume regulation in recovery from intermittent exercise in patients with COPD. *Thorax, 76*(Suppl 1), A11.

Hume, E., Armstrong, M., **Manifield, J.**, & Vogiatzis, I. (2021). P239 The impact of COVID-19 shielding on levels of physical activity and health-related quality of life in COPD patients following pulmonary rehabilitation. *Thorax*, *76*(Suppl 1), A218-A218.

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LIST OF ABBREVIATIONS

$[La^-]_B$	Blood lactate
6MWD	Six-minute walk distance
6MWT	Six-minute walk test
Ab	Abdomen
CHF	Chronic heart failure
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CWR	Constant work rate
EMG	Electromyography
EMT	Expiratory muscle training
FEV_1	Forced expiratory volume in one second
FRC	Functional residual capacity
FVC	Forced vital capacity
IC	Inspiratory capacity
ICC	Intraclass correlation coefficient
IMT	Inspiratory muscle training
IQR	Interquartile range
IRV	Inspiratory reserve volume
LVR	Limb vascular resistance
MAP	Mean arterial blood pressure
Mini-BEST	Mini-balance evaluation systems test
MLSS	Maximum lactate steady state
MVPA	Moderate to vigorous physical activity
O_2	Oxygen
OEP	Optoelectronic plethysmography
P_{ab}	Abdominal pressure
P_{di}	Transdiaphragmatic pressure
PEF	Peak expiratory flow
PE_{max}	Maximal expiratory pressure
PI_{max}	Maximal inspiratory pressure
P_{pl}	Pleural pressure
QB	Quiet breathing
RC	Rib cage
RCa	Abdominal rib cage

RCp	Pulmonary rib cage
RV	Residual volume
SF-36	Short form (36) health survey
SpO_2	Oxygen saturation
T_E	Expiratory time
TFRL	Tapered flow resistive loading
T_I	Inspiratory time
TLC	Total lung capacity
T_{TOT}	Total time
$\dot{V}_A$	Alveolar ventilation
$\dot{V}CO_2$	Carbon dioxide production
$\dot{V}_E$	Minute ventilation
$\dot{V}_{E\ CAP}$	Maximum minute ventilation
$\dot{V}_E/\dot{V}CO_2$	Ventilatory equivalent for carbon dioxide
$\dot{V}_E/\dot{V}_{E\ CAP}$	Available ventilatory capacity
$\dot{V}_E/\dot{V}O_2$	Ventilatory equivalent for oxygen
V_{EE}	End-expiratory volume
V_{EI}	End-inspiratory volume
$\dot{V}O_2$	Oxygen uptake
V_T	Tidal volume
WOB	Work of breathing

ACKNOWLEDGEMENTS

I would firstly like to thank my supervisory team. Specifically, to Dr Gill Barry for her constant guidance and encouragement especially when things did not go to plan (COVID!); to Professor Ioannis Vogiatzis for his expert knowledge of respiratory physiology and for providing me with various opportunities within his research team over the last 4 years; to Dr Katherine Baker and Professor Nicola Adams for their expertise in clinical practice and qualitative research. I will always be grateful for the support and mentorship from this team throughout my PhD.

I would also like to acknowledge the contributions of past and present PhD students. To Dr Nikolaos Chynkiamis for the countless hours he spent explaining the measurement techniques and analyses used in this thesis during the early days, without whom this PhD would have taken me years longer to complete! To Dr Emily Hume, Charikleia Alexiou, and Dimitris Megaritis who kindly assisted with the data collection.

To my parents for their love and support, not only throughout my PhD but my entire life, as well as providing me with the privileged opportunities that have got me to this point. To Ellen, for always believing in me no matter what. The trips to the beach with you and our dog Ralph were a welcome distraction from the stresses that came with undertaking this PhD, and have been my happiest memories of living in the North East.

Finally, I would like to acknowledge the time and commitment of each and every individual that volunteered to be participants over the course of this PhD, without which this research would not have been possible.

DECLARATION OF ORIGINALITY

I declare that the work contained in this thesis has not been submitted for any other award and that it is all my own work. I also confirm that this work fully acknowledges opinions, ideas and contributions from the work of others.

Any ethical clearance for the research presented in this thesis has been approved. Approval has been sought and granted by the Faculty of Health and Life Sciences Ethics committee for each study.

I declare that the word count for this thesis is 45,579 words.

Name: James Manifield

Signature:

Date: 31/05/2022

CHAPTER 1 – INTRODUCTION

1.1. Introduction

It is well established that the population, in all regions of the world, is ageing. The Office for National Statistics (ONS) reported that in mid-2020, 12.5 million people in the UK were aged 65 years and over, equating to ~18% of the population (Park, 2021). Furthermore, the ONS projects that this number will rise to 17.7 million people (24.8% of the population) by 2050. This highlights the need for the development of strategies to promote healthy ageing in older adults.

During the healthy ageing process, most organ systems show a physiological reduction in function (Navaratnarajah & Jackson, 2017). The respiratory system undergoes significant physiological changes with increasing age, including, most importantly, decreased static elastic recoil of the lung, decreased compliance of the chest wall, and decreased respiratory muscle strength (Janssens, Pache, & Nicod, 1999). Respiratory muscle weakness in older adults is associated with the severity of the frailty condition (Pegorari, Ruas, & Patrizzi, 2013), with weaker individuals showing lower physical activity levels (Pegorari et al., 2013), and reduced physical performance (Ohara et al., 2018). The aforementioned physiological changes to the respiratory system during healthy ageing can limit exercise tolerance in older adults due to increased ventilatory demand as well as reduced ventilatory capacity compared to their younger counterparts (Johnson, Reddan, Seow, & Dempsey, 1991a; Molgat-Seon et al., 2018a; Smith, Cross, Van Iterson, Johnson, & Olson, 2018).

One strategy to ameliorate this demand/capacity imbalance of the respiratory system in older adults is to increase the strength and power of the respiratory pump via inspiratory muscle training (IMT; McConnell, 2013). Previous meta-analyses have observed significant improvements in respiratory muscle function, i.e. maximal inspiratory pressure (PI_{max}; reflecting inspiratory muscle strength), and respiratory muscle endurance, along with improved exercise capacity in both healthy (HajGhanbari et al., 2013; Illi, Held, Frank, & Spengler, 2012), and diseased populations (Beaumont, Forget, Couturaud, & Reychler, 2018;

Geddes, O'Brien, Reid, Brooks, & Crowe, 2008; Smart, Giallauria, & Dieberg, 2013) following IMT. To date, however, no meta-analyses on the effects of IMT in healthy older adults have been published.

The underpinning physiological mechanisms of improved exercise tolerance following IMT will be described in depth within chapter 2, but in brief, they have been attributed to reduced respiratory muscle fatigue (Bailey et al., 2010; Romer, McConnell, & Jones, 2002c; Volianitis et al., 2001), improved respiratory muscle efficiency (Turner et al., 2012), reduced effort perception (Griffiths & McConnell, 2007; Ramsook et al., 2017; Romer, McConnell, & Jones, 2002a), attenuated respiratory muscle metaboreflex (McConnell & Lomax, 2006; Witt, Guenette, Rupert, McKenzie, & Sheel, 2007), reduced blood lactate concentrations (McConnell & Sharpe, 2005; Romer, McConnell, & Jones, 2002b; Volianitis et al., 2001), and improved ventilatory parameters (Bailey et al., 2010; Charususin et al., 2016; Petrovic, Reiter, Zipko, Pohl, & Wanke, 2012).

Advances in technology have enabled researchers to investigate total and compartmental thoracoabdominal volumes at rest and during exercise via optoelectronic plethysmography (OEP). This measurement technique allows for the indirect assessment of chest wall surface movement, and can measure breath-by-breath changes of the thoracoabdomen (Parreira et al., 2012). Furthermore, OEP allows for the subdivision of the total thoracoabdominal volume into three compartments: the pulmonary rib cage (RCp), the abdominal rib cage (RCa), and the abdomen (AB; Aliverti & Pedotti, 2002, 2014), whilst taking into consideration the different pressures and muscle groups that act upon these compartments. This includes rib cage muscles such as the intercostals, parasternal, scalene, and neck muscles acting upon the RCp compartment, the diaphragm acting mostly upon the RCa compartment, and both the diaphragm and muscles of the abdominal wall acting upon the AB compartment (Aliverti & Pedotti, 2002; Massaroni et al., 2017).

The acute and chronic effects of inspiratory muscle loading and IMT, respectively, on thoracoabdominal volume regulation (measured via OEP) in healthy older adults remain unclear. Literature surrounding the effects of IMT on breathing pattern and operating lung volumes are inconclusive, with some studies observing significantly increased tidal volume (V_T) and reduced breathing frequency during exercise in chronic obstructive pulmonary disease (COPD) patients (Charususin et al., 2016; Petrovic et al., 2012), and others reporting no significant changes in COPD (Langer et al., 2018) or healthy individuals (Ramsook et al., 2017). Furthermore, recent studies that have utilised OEP to further explore the effects of IMT on compartmental thoracoabdominal volume regulation are limited (Hoffman, Vieira, Silveira, Augusto, & Parreira, 2021; Medeiros et al., 2019) and have only measured these variables during rest.

This thesis, therefore, aims to explore and review the current literature surrounding IMT in healthy older adults, as well as utilise OEP techniques to investigate the acute effects of inspiratory muscle loading, and long-lasting effects of IMT on total and compartmental thoracoabdominal volume regulation during exercise in this population. Specific aims for individual chapters are outlined in chapter 2.

CHAPTER 2 – LITERATURE REVIEW

2.1. Introduction

This chapter will provide a review of the current literature surrounding the topics of this thesis. The respiratory muscles and their contribution to exercise intolerance will initially be outlined in section 2.2. Section 2.3 will cover the age-related changes of the respiratory system, and section 2.4 will describe how these changes may limit exercise tolerance in a healthy ageing population. The various types of, as well as the physiological responses to, acute and chronic IMT will be covered in section 2.5, with specific study aims of this thesis presented in section 2.6.

2.2. The respiratory muscles

The respiratory muscles act in concert to drive expansion and contraction of the chest wall during breathing, and move air into and out of the lungs (De Troyer & Boriek, 2011). Figure 2-1 shows a visual overview of these muscles which will be discussed in more detail within this chapter. These muscles can be divided into muscles of inspiration and muscles of expiration.

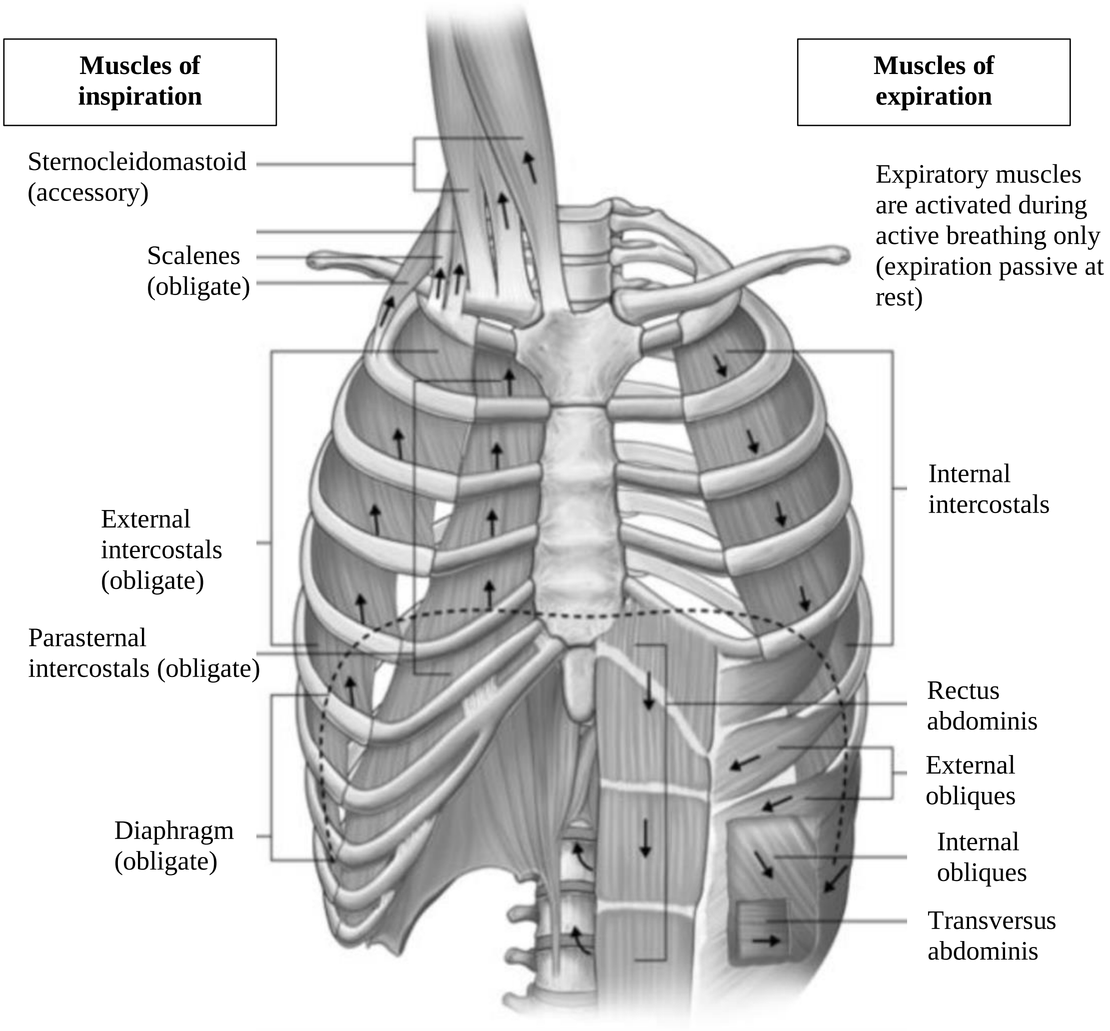


Figure 2-1. Illustration of the respiratory muscles. Adapted from McConnell (2013).

2.2.1. Muscles of inspiration

The principle muscle of inspiration is the diaphragm, a dome-shaped sheet of muscle that separates the thoracic and abdominal cavities (Ratnovsky, Elad, & Halpern, 2008; West, 2012). The muscle fibres radiate from the central tendon and insert peripherally into skeletal structures (De Troyer & Boriek, 2011). These insertions divide the diaphragm into two components: the crural portion, which inserts into the first three lumbar vertebra, and the costal portion, which inserts into the inner surfaces of the lower six ribs (Ratnovsky et al., 2008). During inspiration, diaphragmatic fibres are activated, develop tension and shorten. This causes a descent of the central tendon, pushing the abdominal visceral caudally, displacing the abdominal wall outward, and expanding the thoracic cavity (De Troyer & Boriek, 2011; De Troyer et al., 2005; Ratnovsky et al., 2008).

The other main muscles during inspiration are the external intercostal muscles and are formed by a thin layer of muscle fibres in the intercostal spaces. They are obliquely oriented, in the caudal-ventral direction from each rib to the one below (De Troyer et al., 2005; Ratnovsky et al., 2008; Figure 2-2A). The primary effect of the contraction of intercostal muscles is to displace the ribs and alter the configuration of the rib cage (De Troyer et al., 2005), with external intercostal muscles contracting to raise the rib cage (Ratnovsky et al., 2008). Based on the theory of Hamberger (1749), due to their lower insertion being further from the axis of rotation of the ribs than their upper insertion, meaning when these fibres contract, the torque acting on the lower rib is greater than that acting on the upper rib (De Troyer & Boriek, 2011).

The parasternal intercostals are obligate inspiratory muscles located ventrally, between the sternum and chondrocostal junctions, where external intercostals are replaced by a fibrous aponeurosis and the anterior intercostal membrane (De Troyer et al., 2005). The parasternal intercostals are a portion of the internal intercostals which have an inspiratory rather than expiratory function (De Troyer et al., 2005), with these muscles acting to expand the chest wall, whilst also stabilising the rib cage against the negative swings in intrathoracic pressure caused by the contracting diaphragm (Decramer & De Troyer, 1984).

The scalene muscles are also obligate respiratory muscles contributing to expand the rib cage and lung (De Troyer & Estenne, 1984). The scalene muscles consist of three bundles running from the transverse processes of the lower five cervical vertebrae and insert into the upper surface of the first two ribs (Han, Gayan-Ramirez, Dekhuijzen, & Decramer, 1993; Ratnovsky et al., 2008).

Accessory muscles of inspiration include the sternocleidomastoid which flex the neck and rotate the head (Han et al., 1993). This muscle, along with the scalene, becomes more active in their role within the process of respiration when ventilatory demand is increased, i.e. during exercise, (Raper, Thompson Jr, Shapiro, & Patterson Jr, 1966). The sternocleidomastoid can be divided into four portions: the sterno-mastoid, sterno-occipital, cleido-mastoid, and cleido-occipital and divides the neck area into anterior and posterior triangles (Kennedy, Albert, & Nicholson, 2017). This muscle originates on the medial third of the clavicle and the ventral aspect of the manubrium sterni and inserts onto the mastoid process on the skull. These muscles act mainly during moderate and deep inspiration (Nepomuceno, Nepomuceno, Regalo, Cerqueira, & Souza, 2014), and assist in expanding the rib cage by raising the sternum and first two ribs (Legrand, Schneider, Gevenois, & De Troyer, 2003).

2.2.2. Muscles of expiration

During quiet breathing (QB), expiration is a passive process and expiratory muscles remain inactive. The elastic properties of the lung and chest wall allow them to return to their equilibrium positions after being actively expanded during inspiration (West, 2012). During circumstances of increased ventilation, such as during exercise or voluntary hyperventilation, expiration becomes active.

The main expiratory muscles are those forming the abdominal wall and include the rectus abdominis, the external oblique, the internal oblique, and the transversus abdominis (De Troyer & Boriek, 2011). The rectus abdominis is the most ventral and extends caudally down the abdominal wall from the ventral sternum and the fifth sixth and seventh costal cartilages to the pubis (De Troyer & Estenne, 1988; Ratnovsky et al., 2008). The external oblique muscle originates from external surfaces of the lower eight ribs with its fibres running downward and ventrally into the iliac crest, inguinal ligament and linear alba (De Troyer & Boriek, 2011). The internal oblique is deep to the external oblique and runs from the iliac crest and inguinal ligament to the anterolateral surface of the last three rib cartilages into the linear alba (Ratnovsky et al., 2008). The transversus abdominis is the deepest of these muscles running circumferentially from the inner surface of the lower six ribs, the lumbar fascia, iliac crest and inguinal ligament into the rectus sheath (Ratnovsky et al., 2008).

The internal intercostal muscles of the rib cage are also involved in expiration and, like the external intercostal muscles, are located between adjacent ribs. The muscle fibres run in the caudal-dorsal direction from the rib above to the rib below and are located deep to the external intercostal muscles (De Troyer et al., 2005; Ratnovsky et al., 2008; Figure 2-2B). The contraction of these muscles act to lower the ribs, as the torque acting on the upper rib is greater than that acting on the lower rib (De Troyer et al., 2005).

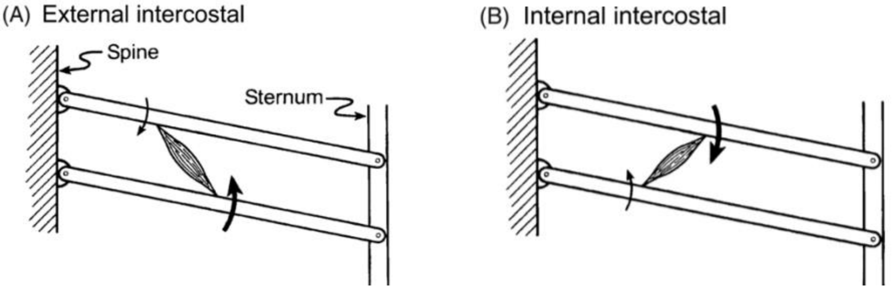


Figure 2-2. Diagram showing the actions of intercostal muscles. Adapted from De Troyer et al. (2005).

2.2.3. Mechanics of rib cage motion

The reciprocity theorem of mechanics (Maxwell, 1864), when applied to the respiratory system, predicts that the respiratory effect of a muscle (change in airway pressure [ΔP_{ao}] produced during a maximal isolated contraction against a closed airway) is related to the mass of the muscle (m), the active muscle tension per unit cross-sectional area (σ), and the fractional change in muscle length (ΔL/L) per unit increase in volume of the relaxed chest wall $(\Delta V_L)_{Rel}$ (De Troyer et al., 2005):

$$\Delta P_{ao} = m\ \sigma\ (\Delta L/[L\Delta V_L])_{Rel}$$

The mechanical advantage of a respiratory muscle can be defined as $\Delta P_{ao}/m\sigma$, and can be evaluated by measuring $(\Delta L/[L\Delta V_L])_{Rel}$. Therefore, a muscle that shortens during passive inflation (negative $\Delta L/L$) would have an inspiratory mechanical advantage, causing a fall in P_{ao} during isolated contraction, and a muscle that lengthens during passive inflation (positive $\Delta L/L$) would have an expiratory mechanical advantage, causing a rise in P_{ao} during isolated contraction (De Troyer et al., 2005).

The external intercostals in the dorsal portion of rostral interspaces have a large inspiratory mechanical advantage, with this advantage decreasing in the ventral and caudal direction (the ventral portion of caudal interspaces) where it reverses into an expiratory mechanical advantage (De Troyer et al., 2005). This distribution of mechanical advantage in intercostal muscles is caused by two mechanisms which are illustrated in Figure 2-3. The first depending on the nonuniform coupling between rib displacement and lung expansion and the consequent effects of equal and opposite forces on adjacent ribs (De Troyer & Boriek, 2011; De Troyer et al., 2005; Figure 2-3A). In the rostral interspace, the decrease in P_{ao} caused by the cranial displacement of a rib is larger than the increase in P_{ao} caused by the caudal displacement of the rib above. Whereas, in the caudal interspace, the decrease in P_{ao} caused by the cranial displacement of a rib is smaller than the increase in P_{ao} caused by the caudal displacement of the rib above. The external and internal intercostals in the rostral interspaces, therefore, have an inspiratory bias, and those in the caudal interspaces have an expiratory bias (De Troyer & Boriek, 2011; De Troyer et al., 2005).

The second mechanism is based on the Hamberger theory and adjusted to account for the three-dimensional configuration of the rib cage (Figure 2-3B). It is the result of the difference between magnitudes and moments applied by the muscles to the upper and lower ribs of the interspace (De Troyer et al., 2005). In the dorsal part, the difference confers to the external intercostal an inspiratory mechanical advantage and to the internal intercostal an expiratory mechanical advantage. Due to the curvature of the ribs, the mechanical advantages of these muscles decrease in the ventral direction, and in the sternum vicinity, the internal (parasternal) intercostal has an inspiratory mechanical advantage (De Troyer & Boriek, 2011; De Troyer et al., 2005)

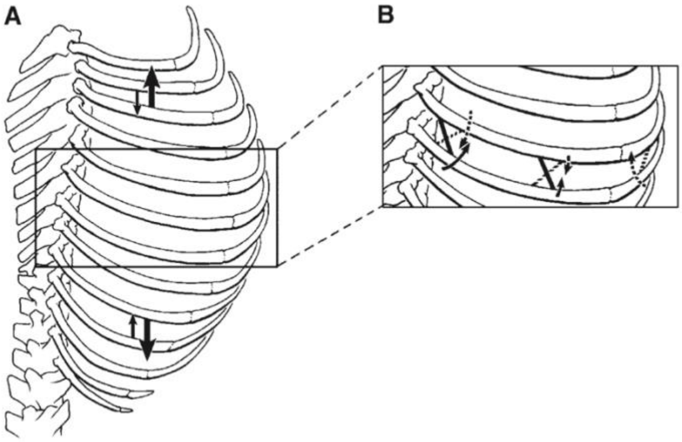


Figure 2-3. Diagram showing the two mechanisms responsible for the distribution of mechanical advantage of the intercostal muscles. Adapted from De Troyer et al. (2005).

2.2.4. *Exercise and the respiratory muscles*

During exercise, alveolar ventilation ($\dot{V}_A$) must increase in proportion to muscular oxygen consumption ($\dot{V}O_2$) and CO_2 production ($\dot{V}CO_2$); and the increased breathing frequency, minute ventilation ($\dot{V}_E$) and work of breathing (WOB) caused by exercise hyperpnoea places a significant demand on the respiratory muscles (Welch, Kipp, & Sheel, 2019). Furthermore, the demand for blood flow and O_2 transport is increased due to contraction of the respiratory muscles, meaning that the gas transport needs of both locomotor and respiratory muscles must be considered.

Non-invasive measurements of chest wall kinematics have allowed researchers to investigate the breath-by-breath changes of lung- and diaphragm-apposed sections of the rib cage along with abdominal compartments, and the regulation of these thoracoabdominal compartments during rest and exercise (Aliverti et al., 1997; Kenyon et al., 1997). One such measurement technique is OEP. A detailed description of this method can be found in chapter 4, but in brief, this system involves an optical tracking system that detects the movement of surface markers on the chest wall, allowing for non-invasive measurements of V_T and end-inspiratory (V_{EI}) and end-expiratory volumes (V_{EE}; Kenyon et al., 1997; Parreira et al., 2012).

Early studies have combined the measurements of thoracoabdominal volumes, measured via OEP, with simultaneous measurements of pleural (Ppl) and abdominal (Pab) pressures during exercise (Aliverti et al., 1997). These recordings have suggested that the diaphragm acts mainly as a flow generator during exercise, meaning that its mechanical power is mainly expressed as velocity of shortening rather than pressure (Aliverti, 2016; Aliverti et al., 1997). Rib cage and abdominal muscles, on the other hand, act primarily as pressure generators. Rib cage muscles develop the pressures to displace the rib cage and increase V_{EI}, whereas abdominal muscles provide pressures to displace the abdomen and decrease V_{EE} (Aliverti et al., 1997).

The action of the inspiratory and expiratory muscles during exercise are highly coordinated. During inspiration as the rib cage muscles contract, the abdominal muscles gradually relax, and vice versa during expiration (Aliverti, 2016). This prevents rib cage distortion, unloads the diaphragm allowing it to act as a flow generator, and decreases abdominal volume below resting levels (Aliverti et al., 1997; Henke, Sharratt, Pegelow, & Dempsey, 1988).

This reduction of V_{EE} (and functional residual capacity; FRC) due to active expiration during exercise increases the length of diaphragm fibres placing them at a more favourable length-tension relationship and allowing for more pressure generation for a given neural output (Henke et al., 1988; Martin, Aubier, & Engel, 1982). The mechanics of breathing is therefore optimised during exercise as V_T occurs in the most compliant part of the respiratory system, reducing inspiratory work by allowing the elastic energy stored from the active contraction of abdominal muscles during expiration to be used during the subsequent inspiration (Aliverti, 2016; Henke et al., 1988). Furthermore, accessory muscles of the respiratory system are progressively recruited with increasing ventilatory demand, sharing the increased load needed to support exercise hyperpnea (Dempsey, Romer, Rodman, Miller, & Smith, 2006).

2.2.5. Respiratory muscle contribution to exercise intolerance

2.2.5.1. Diaphragmatic work

In most untrained healthy individuals, inspiratory muscle pressure generation during a maximal incremental exercise test is around 40–50% of maximum dynamic capacity (Dempsey, La Gerche, & Hull, 2020; Johnson, Saupe, & Dempsey, 1992), and the oxygen cost of exercise hyperpnoea is 3–6% of total body $\dot{V}O_2$ achieved in moderate exercise rising to around 10% of $\dot{V}O_{2\,\max}$ achieved during heavy exercise (Aaron, Seow, Johnson, & Dempsey, 1992).

Unlike normal healthy individuals, the pressure generated by the inspiratory muscles during high intensity exercise can approach maximum, and airways can undergo dynamic compression causing expiratory flow limitation in highly fit endurance athletes (Aliverti, 2016), older adults (Turner, Mead, & Wohl, 1968), and COPD patients (Aliverti, 2008). To avoid dynamic compression of the airways and subsequent expiratory flow limitation during high intensity exercise, V_{EE} is forced upward, resulting in “dynamic hyperinflation”, to allow further increases in flow (Aliverti, 2016; Klas & Dempsey, 1989).

Dynamic hyperinflation can be regarded as a compensatory mechanism by which higher lung volumes can be reached and higher expiratory flow rates can be achieved to reduce expiratory time (Vogiatzis & Zakynthinos, 2012). At these higher operating lung volumes, the inspiratory muscles must overcome higher elastic load from the lung and chest wall (Agostoni & Rahn, 1960), whilst being put at a mechanical disadvantage due to the flattened curvature of the diaphragm, shortening its resting length and reducing its force-generating capacity (Sheel & Romer, 2012). In these conditions, the capacity of the respiratory system may be met or exceeded, with around 16% of the total $\dot{V}O_{2\ max}$ and total cardiac output devoted to the respiratory muscles during maximal exercise (Aaron et al., 1992; Harms et al., 1998).

Volitional measures of global respiratory muscle fatigue include maximal inspiratory (PI_{max}) and expiratory (PE_{max}) pressure manoeuvres using a pressure transducer. These simple measurements reflect the global pressure generating capacity of the respiratory muscles, and an observed transient decrease in this pressure following exercise can define respiratory muscle fatigue (Sheel & Romer, 2012). Previous studies utilising these measurements have indeed observed significantly reduced maximal respiratory pressures following high-intensity exercise (Griffiths & McConnell, 2007; Romer et al., 2002c; Volianitis et al., 2001).

Non-volitional measures of respiratory muscle fatigue, including electrical and magnetic stimulation of the phrenic nerves, have confirmed the contractile fatigue of the diaphragm (15–30% reduction of pre-exercise transdiaphragmatic pressure; P_{di}) immediately following heavy exercise (>80% $\dot{V}O_{2\ max}$) sustained to exhaustion, with values not returning to baseline levels until 1–2 hours post-exercise (Babcock, Pegelow, Taha, & Dempsey, 1998; Johnson, Babcock, Suman, & Dempsey, 1993; Mador, Magalang, Rodis, & Kufel, 1993). This fatigue may, in part, be due to the high levels of work sustained by the diaphragm during high intensity exercise, due to findings that when diaphragmatic work is reduced during exercise via proportional assist ventilation, diaphragmatic fatigue does not occur (Babcock, Pegelow, Harms, & Dempsey, 2002; Dempsey et al., 2006). Furthermore, fatigue does not occur when the magnitude and duration of diaphragmatic work achieved during exercise is mimicked by resting participants using visual and auditory cues, and only occurred when pressures are voluntarily increased twofold greater than required during exercise intensities that resulted in exercise-induced diaphragmatic fatigue (Babcock, Pegelow, McClaran, Suman, & Dempsey, 1995) suggesting further mechanisms are at play.

2.2.5.2. Cardiorespiratory interactions and the respiratory muscle metaboreflex

The lower threshold for diaphragmatic fatigue during whole-body exercise compared to the higher threshold at rest can be explained by the competition for available blood flow between the diaphragm and locomotor muscles during high-intensity exercise, thus promoting inadequate oxygen transport and fatigue of the diaphragm (Dempsey et al., 2006; Romer & Polkey, 2008). Fatiguing respiratory muscles can cause increased sympathetic vasoconstrictor outflow via a supra-spinal reflex (metaboreflex), and reduce vascular conductance and perfusion of locomotor muscles, which may provide an insight into how respiratory muscles can limit exercise performance (Harms, 2007; Romer & Polkey, 2008).

Evidence from animal studies has shown that both limb skeletal muscles and respiratory muscles (such as the diaphragm) are richly innervated by group III and IV afferent nerve fibres, which act as metaboreceptors (Duron, 1981). When these phrenic nerve afferents are stimulated via electronically or chemically induced fatiguing diaphragmatic contractions, a time-dependent increase in single and multiunit activity has been observed in anaesthetised cats (Balzamo, Lagier-Tessonnier, & Jammes, 1992) and rats (Hill, 2000). Furthermore, a transient infusion of lactic acid into the diaphragm via the phrenic artery in resting and exercising dogs increased mean arterial blood pressure (MAP) and reduced hind-limb blood flow and vascular conductance (Rodman, Henderson, Smith, & Dempsey, 2003).

This mechanism of working respiratory muscles eliciting increases in sympathetic vasoconstrictor outflow to the limb skeletal muscles has also been found in humans (Sheel et al., 2001; St Croix, Morgan, Wetter, & Dempsey, 2000). The participants within the study conducted by St Croix et al. (2000) were required to breathe against inspiratory resistance (equal to 60% PI_{max}) to task failure at a prolonged duty cycle (inspiratory time [T_I]/total time [T_{Tot}]; 0.70) and constant breathing frequency of 15 breaths/min. The authors observed a time-dependent increase in muscle sympathetic nerve activity in the resting leg during high levels of inspiratory muscle force output using a prolonged duty cycle which limited perfusion. Manipulation of V_T , duty cycle or central respiratory motor output in the absence of fatigue did not affect muscle sympathetic nerve activity, so a reflex arising within the fatiguing respiratory muscles was attributed to the changes observed (St Croix et al., 2000). A follow-up study, conducted by the same research group, investigated whether limb muscle vasoconstriction and reduced limb blood flow would also be observable during inspiratory muscle fatigue (Sheel et al., 2001). The authors found a time-dependent decrease in resting leg blood flow and an increase in limb vascular resistance (LVR) during high levels of inspiratory muscle force, and, as in their previous study, found no changes in the measured variables when central respiratory motor force output was augmented in the absence of fatigue (Sheel et al., 2001). This work further suggests that these changes are attributed to a “metaboreflex” originating in the fatiguing inspiratory muscles.

During maximal cycle ergometer exercise, researchers investigated the effects of increasing or decreasing the WOB on limb blood flow and LVR (Harms et al., 1997) and cardiac output (Harms et al., 1998) compared to a control trial where WOB was not manipulated. In the first of these studies, it was observed that, when inspiratory work was reduced via a proportional-assist ventilator, leg blood flow increased by 4.3%, and when inspiratory work was increased via resistive loading, leg blood flow decreased by 7% (Harms et al., 1997).

In a subsequent study, the researchers observed significantly lower cardiac output values during unloaded inspiratory work at maximal exercise compared to control values, along with no change in cardiac output between control and inspiratory loaded breathing (Harms et al., 1998). Correctional analysis implied that the reduced cardiac output during inspiratory muscle unloading was due to decreased metabolic demands of the respiratory muscles and/or decreased intrathoracic pressures on venous return. The authors concluded that, at maximal exercise under normal physiological conditions, the respiratory muscles require around 14–16% of cardiac output to meet their metabolic requirements. Combined, the findings from these two studies suggest that, due to respiratory muscle reflex-induced sympathetically mediated vasoconstriction, limb blood flow is reduced to working locomotor muscles when the WOB is increased during maximal exercise (Harms et al., 1998).

This evidence of an inspiratory muscle metaboreflex has also been supported in more recent studies (Katayama et al., 2019; Katayama, Iwamoto, Ishida, Koike, & Saito, 2012; McConnell & Lomax, 2006; Smith et al., 2017a; Wetter, Harms, Nelson, Pegelow, & Dempsey, 1999). In summary, high-intensity exercise (Wetter et al., 1999), or moderate-intensity exercise combined with inspiratory muscle loading (Katayama et al., 2012), can lead to an inspiratory muscle metaboreflex which is activated when metabolite accumulation stimulates type III and IV afferent nerve fibres to increase firing frequency. This causes increased sympathetic efferent outflow, inducing vasoconstriction, and limiting blood flow, and consequently restricting the supply of oxygen to, and removal of metabolites from, exercising muscles, resulting in accelerated limb fatigue and impaired exercise performance (Dempsey et al., 2006; Romer, Lovering, Haverkamp, Pegelow, & Dempsey, 2006; Romer & Polkey, 2008).

2.3. Age-related changes to the respiratory system

During the healthy ageing process, the respiratory system undergoes physiological changes including a decrease in compliance of the chest wall, a decreased static elastic recoil of the lung, and a decrease in respiratory muscle strength (Janssens et al., 1999).

The stiffening of the chest wall is related to the calcification of costal cartilage and decalcification of the ribs and vertebrae (Krumpe, Knudson, Parsons, & Reiser, 1985). This results in reduced mobility of the chest wall and thus a greater abdominal and diaphragmatic contribution to ventilation in older adults compared to young adults (Janssens, 2005). An average loss of 0.1–0.2 cmH_2O per year in static elastic recoil pressure of the lung from age 20 to 60 is also a consequence of healthy ageing (Turner et al., 1968), and is potentially caused by alterations in the crosslinking or spatial arrangement of the elastic fibre network and reduced surface tension forces of the alveoli (Janssens et al., 1999; Miller, 2010). The diameter of alveolar ducts increase with age and alveoli become shallower and wider (Verbeken et al., 1992). Less elastic recoil also causes a reduction in maximal expiratory flow rates in older adults (DeLorey & Babb, 1999).

The decrease in elastic recoil of the lung and increased rigidity of the chest wall in older adults has been termed “senile emphysema” and, combined with reduced elastic attachments of supporting alveoli, causes the smaller airways to close at higher lung volumes, shifting an individual’s pressure-volume curve of the lung upwards and to the left (Frank, Mead, & Ferris, 1957; Janssens et al., 1999; Taylor & Johnson, 2010). This therefore results in an increased FRC and residual volume (RV) in older adults (Crapo, Morris, Clayton, & Nixon, 1982), causing them to breathe at higher lung volumes than their younger counterparts.

An increased age-related elastic load from the chest wall is associated with the increase in FRC due to the shape of the static pressure-volume curve of the respiratory system (Janssens et al., 1999; Turner et al., 1968). A 60-year-old individual would, therefore, have to do around 20% more elastic work at a given ventilation than a 20-year-old individual (Turner et al., 1968), meaning that the respiratory muscles of older adults must work harder due to acting on a less compliant chest wall.

2.3.1. Age-related changes in respiratory muscle function

Significant age-related decreases in respiratory muscle strength have been observed previously (Enright, Kronmal, Manolio, Schenker, & Hyatt, 1994; Polkey et al., 1997; Tolep, Higgins, Muza, Criner, & Kelsen, 1995; Watsford, Murphy, & Pine, 2007). Polkey et al. (1997) and Tolep et al. (1995) measured transdiaphragmatic pressure (P_{di}) in younger and older adults. During a maximal sniff (sniff P_{di}) with bilateral cervical magnetic stimulation of the phrenic nerve roots ($P_{di,\ tw}$), Polkey et al. (1997) observed reduced values in the older adults compared their younger counterparts for both sniff P_{di} (13%) and $P_{di,\ tw}$ (23%). Furthermore, Tolep et al. (1995) reported reduced diaphragmatic strength (reflected by P_{di} max) of ~25% in older adults compared to younger adults. Polkey et al. (1997) observed a mean $P_{di,\ tw}$ in older adults of 26.8 cmH_2O compared to 32.5 cmH_2O in younger adults (equating to a median reduction of 8 cmH_2O). At a stimulating frequency of 10 Hz, older adults tended to generate a higher fraction of P_{di} obtained at 100 Hz than their younger counterparts, however, this trend was not statistically significant (Polkey et al., 1997). The authors concluded that ageing is associated with a reduction in diaphragm strength, however, the magnitude of this reduction in small and may be attenuated by a leftward shift of the force-frequency relationship (Polkey et al., 1997). Guidelines on respiratory muscle testing have suggested a threshold bilateral $P_{di,tw}$ of <20 cmH_2O for clinically significant weakness (Laveneziana et al., 2019), implying that the participants within the study by Polkey et al. (1997) did not have pathological weakness of the diaphragm.

This begs the question as to whether weakness of the respiratory muscles in older adults is functionally important. If the mechanical load on the respiratory muscles is substantial in older adults (due to decreased compliance of the chest wall and increased WOB; discussed below) then it is likely that even minor reductions in respiratory muscle strength (reduced capacity) may be functionally important and cause a significant increase in the load:capacity ratio of the respiratory muscles leading to breathlessness and increases in ventilatory drive (Moxham & Jolley, 2009).

Respiratory muscle strength has also been measured via maximal inspiratory (PI_{max}) and maximal expiratory pressure (PE_{max}) manoeuvres in older adults (Enright et al., 1994; Watsford et al., 2007), with these studies also observing reduced respiratory muscle strength with ageing. Specifically, Enright et al. (1994) observed decreases in maximal respiratory pressures in adults aged 65 to 85 years of between 0.8 and 2.8 cmH_2O per year.

Respiratory muscle weakness in older adults has been associated with the severity of the frailty condition, and decreased hand-grip strength and physical activity levels (Pegorari et al., 2013). In addition, inspiratory and expiratory muscle strength is also positively correlated with other sarcopenia indicators such as skeletal muscle mass index (Shin et al., 2017) and gait speed (Ohara et al., 2018), suggesting that respiratory muscle strength interferes with physical performance in older adults. Components of the frailty syndrome can accelerate the sarcopenia progress and intensify the negative impact on respiratory muscle strength (Pegorari et al., 2013). Furthermore, both PI_{max} and PE_{max} are associated with self-reported general health in older adults, with individuals who reported poor or fair health showing significantly lower values of respiratory muscle strength than those who reported good, very good, or excellent health (Enright et al., 1994).

2.4. Factors limiting exercise tolerance in healthy older adults

2.4.1. Ventilatory responses to exercise

The aforementioned changes in structural and functional alterations of the respiratory system with ageing can limit exercise tolerance in older adults, and it is well established within the literature that there are increased ventilatory requirements during exercise within this population (Jensen, Ofir, & O'Donnell, 2009; Johnson et al., 1991a; Johnson, Reddan, Pegelow, Seow, & Dempsey, 1991b; Molgat-Seon et al., 2018a; Patrick, Bassey, & Fentem, 1983).

Previous studies (Brischetto, Millman, Peterson, Silage, & Pack, 1984; Faisal et al., 2015; Jensen et al., 2009; Johnson et al., 1991b; McConnelll & Davies, 1992) have shown that, compared to their younger counterparts, older adults have a higher $\dot{V}_E$, and ventilatory equivalents for both oxygen ($\dot{V}_E/\dot{V}O_2$) and carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) These changes reflect the combination of increased physiological dead space (Mummery et al., 2003), ventilation-perfusion mismatching (Wagner, Laravuso, Uhi, & West, 1974), an earlier onset of lactic acidosis (or reduced anaerobic threshold), and reduced mechanical efficiency of locomotor muscles (Jensen et al., 2009; Roman, Rossiter, & Casaburi, 2016). Furthermore, older adults have a lower maximum minute ventilation ($\dot{V}_{E\ CAP}$) and utilise a higher fraction of their available ventilatory capacity ($\dot{V}_E/\dot{V}_{E\ CAP}$) at rest and during exercise (Molgat-Seon et al., 2018a).

As older individuals have been observed to have increased ventilatory demand (i.e. higher $\dot{V}_E$ for a given absolute work rate) along with reduced ventilatory capacity (i.e. lower $\dot{V}_{E\ CAP}$) than younger individuals, this can lead to increases the likelihood of older adults reaching the mechanical limits of the respiratory system at a given work rate (Molgat-Seon et al., 2018a).

2.4.2. Operational lung volume regulation

As explained previously, during exercise, healthy young individuals are capable of reducing V_{EE} below FRC via active expiratory muscle recruitment (Johnson et al., 1992; Vogiatzis et al., 2005). This results in a more optimal inspiratory muscle length and allows the expansion of V_T to occur by encroachment into both inspiratory and expiratory reserve volumes (Smith, Kurti, Meskimen, & Harms, 2017b; Vogiatzis & Zakynthinos, 2012). Expiratory flow limitation (caused by age-related structural alterations, i.e., reduced elastic recoil pressure) can prevent decreases in V_{EE} during exercise in older adults (Babb & Rodarte, 2000; DeLorey & Babb, 1999; Vogiatzis & Zakynthinos, 2012), and, consequently, results in V_T expansion occurring due to encroachment into the inspiratory reserve volume (IRV) only (Vogiatzis & Zakynthinos, 2012). Expiratory flow limitation can also occur in healthy young adults during exercise (Guenette, Witt, McKenzie, Road, & Sheel, 2007; Johnson et al., 1992) causing an increased V_{EE} at maximal intensities due to individuals approaching their mechanical limits to generate expiratory flow, avoid any dynamic compression of the airways, and minimise expiratory flow limitation (Dominelli, Guenette, Wilkie, Foster, & Sheel, 2011).

The variability in the decrease of V_{EE} during exercise in older populations, however, should be noted. Previous studies have shown similar operating lung volumes between younger and older adults (Faisal et al., 2015), an earlier increase in V_{EE} during incremental exercise in older adults compared to younger adults (McClaran, Babcock, Pegelow, Reddan, & Dempsey, 1995;

Smith et al., 2017b), and even increased V_{EE} at maximal intensities in younger adults only (Wilkie, Guenette, Dominelli, & Sheel, 2012). Wilkie et al. (2012) suggested that "impending expiratory flow limitation" may have altered the V_{EE} regulation in the older individuals due to expiration being reflexively terminated prematurely in response to a minimal level of expiratory flow limitation at low lung volumes. This finding, however, contrasts with studies showing a higher V_{EE} throughout submaximal and maximal exercise in older adults compared to their younger counterparts (Molgat-Seon et al., 2018a).

A similar response was observed in V_{EE} regulation between younger and older adults during maximal exercise (Molgat-Seon et al., 2018a), whereby, most older adults reduced V_{EE} until they approached expiratory flow limitation, at which point V_{EE} increased towards resting values in order to avoid mechanical constraint (Johnson et al., 1991b). It was also reported that 7 out of 22 older adults but none of the younger subjects showed an increase in V_{EE} during exercise above resting values (>0.15 L) suggesting evidence for dynamic hyperinflation in the ageing population.

Molgat-Seon et al. (2018a) also reported higher V_{EI} in older adults during submaximal exercise but similar to younger adults at maximal exercise. Greater V_{EI} (as a percentage of forced vital capacity; %FVC) in older adults during exercise have also been reported by Smith et al. (2017b). The authors suggested that this may have been caused by earlier increases in V_{EE}, and likely reduced dynamic compliance and contributed to greater WOB (Johnson, Badr, & Dempsey, 1994; Smith et al., 2017b). Regardless of age, however, peak V_{EI} during exercise observed by Molgat-Seon et al. (2018a) was ~90% of total lung capacity (TLC), with the authors explaining that this was likely due to the sigmoidal shape of the pressure-volume curve within the respiratory system, therefore, any further increase in V_{EI} would substantially increase the WOB. The authors concluded that older adults regulated their operating lung volumes similar to their younger counterparts but at higher fractions of TLC (Molgat-Seon et al., 2018a).

2.4.3. Work of breathing (WOB) and inspiratory muscle activation patterns during exercise

Increases in dynamic operating lung volumes, along with additional age-related structural and functional factors, leads to greater elastic and flow-resistive WOB in older adults (Smith et al., 2018). At ventilations ($\dot{V}_E$) >50 L/min, older adults have a significantly higher WOB compared to their younger counterparts (Molgat-Seon et al., 2018a; Smith et al., 2018).

In the study conducted by Smith et al. (2018), the authors partitioned the WOB into the inspiratory and expiratory resistive, and inspiratory elastic WOB to further determine the mechanisms behind age-related increases in total WOB. Both inspiratory and expiratory resistive, and inspiratory elastic WOB was significantly greater in older adults compared to younger adults, with the largest contribution to total WOB arising from the inspiratory elastic WOB in older adults (Smith et al., 2018). The authors attributed this to the participants adopted ventilatory strategy, in that older adults had a reduced IRV, greater tidal volume/inspiratory capacity ratio (V_T/IC), and associated decreased dynamic lung compliance and increased WOB at $\dot{V}_E$ of 75 L/min (Smith et al., 2018). It was suggested that, although IRV (%FVC) and dynamic lung compliance was significantly less in older adults compared to younger adults during exercise, the resulting increase in elastic WOB was likely less that what would have been observed if participants adopted a higher breathing frequency and thus inspiratory resistive WOB for a given $\dot{V}_E$.

The greater inspiratory and expiratory resistive WOB in older compared to younger individuals during exercise was attributed to age-related anatomical differences, such as reduced bronchial diameter, and therefore increased airway resistance (Niewoehner & Kleinerman, 1974; Smith et al., 2018). This meant that, at matched $\dot{V}_E$, the higher inspiratory pressure generation by older adults did not result in greater mean inspiratory flows (Smith et al., 2018). Furthermore, expiratory resistive WOB was likely caused by the smaller airways in older adults, which are associated with expiratory flow limitation development during exercise, further increasing airway resistance via dynamic compression (Guenette et al., 2007). Older individuals who exhibit expiratory flow limitation at $\dot{V}_E$ of 75 L/min, therefore, have significantly greater expiratory resistive WOB than those who do not (Smith et al., 2018).

The greater WOB in older adults requires increased inspiratory muscle activation, evidenced by Molgat-Seon et al. (2018b), who observed greater diaphragm activation (measured via electromyography; EMG_{di}) at absolute $\dot{V}_E$ of 30, 50, and 70 L/min^{-1}, greater sternocleidomastoid activation (EMG_{scm}) at absolute $\dot{V}_E$ of 50 and 70 L/min^{-1}, and similar scalene activation (EMG_{sca}) at absolute $\dot{V}_E$ of 30, 50 and 70 L/min^{-1} compared to younger adults. When comparisons were made as a function of relative $\dot{V}_E$, older adults had similar EMG_{di}, a lower EMG_{sca} at 40, 60, and 80% peak $\dot{V}_E$, and a higher EMG_{scm} at 40% peak $\dot{V}_E$ than their younger counterparts. As observed previously (Campbell, 1955), the sternocleidomastoid becomes active once V_T encroaches on around 70% of IC, which, due to the age-related reduction in ventilatory efficiency, is likely to occur at a lower absolute and relative $\dot{V}_E$ in older adults (Molgat-Seon et al., 2018b).

The authors conclude that the increased pressure required to generate a given $\dot{V}_E$ during exercise in older adults was achieved via recruitment of the diaphragm and extradiaphragmatic muscles to a greater extent than in younger adults. The absence of age-related differences in inspiratory pressure generation at relative fractions of peak $\dot{V}_E$, however, implies that the effects of age on inspiratory muscle activation may also be related to other factors, including respiratory kinematics and/or respiratory muscle efficiency (Molgat-Seon et al., 2018b).

2.4.4. Respiratory muscle metaboreflex activation

A higher WOB in older adults may have significant implications regarding the competition for available cardiac output between exercising respiratory and locomotor muscles. Furthermore, older adults have less inspiratory muscle fatigue resistance compared to their younger counterparts which is likely due to the reduced number of fatigue-resistant muscle fibres during the ageing process (Chen & Kuo, 1989). The combined age-related changes in respiratory muscle function suggest that older adults would exhibit an exaggerated inspiratory muscle metaboreflex compared to younger adults, however, this is only the case in women and not men (Smith et al., 2017a).

When 16 young adults (8 young men and 8 young women) and 16 older adults (8 older men and 8 older women) performed inspiratory resistive breathing tasks at 65% PI_{max}, Smith et al. (2017a) observed significantly greater increases in MAP and LVR, along with significantly greater decreases in limb blood flow in the older women compared to the younger women. No significant age-related differences were observed in these variables for men, nor between older men and older women. Collectively, these findings suggest greater inspiratory muscle metaboreflex-induced cardiovascular consequences in older women, with the authors proposing greater sympathetic vasoconstriction during exercise (Fadel et al., 2004) and/or greater transduction of sympathetic outflow to the peripheral vasculature (Hart et al., 2011) in older women as potential mechanisms (Smith et al., 2017a).

Previous work from this group has shown that younger women have an attenuated inspiratory muscle metaboreflex compared to younger men (Smith et al., 2016). One potential explanation for this sex difference may be the greater percentage of type I muscle fibres in women, and the possibility of women exhibiting a greater percentage of type I/IIa muscle fibres in the diaphragm (Smith et al., 2016). This would contribute to attenuated metabolite production, decreased type III/IV afferent nerve stimulation, and thus greater inspiratory muscle fatigue resistance in women (Smith et al., 2016).

Studies in rats have shown that intercostal blood flow and vascular conductance is increased during submaximal exercise in older rats compared to young rats, indicating that accessory respiratory muscle blood flow control is altered during the ageing process (Smith, Hageman, Harms, Poole, & Musch, 2019). The optimal length of the length-tension relationship for the intercostal muscles is near TLC (Decramer, 1997), which, as FRC is increased with ageing

(Crapo et al., 1982), allows for a more advantageous respiratory pressure development by these muscles. No age-related differences in diaphragm blood flow was observed by Smith et al. (2019), with the authors attributing this to decreased contribution of the diaphragm to total respiratory pressure with increasing ventilation during exercise (Molgat-Seon et al., 2018b). Furthermore, breathing at higher lung volumes is disadvantageous for the diaphragm muscle, due to its optimal muscle length being near to FRC (Decramer, 1997). Accessory respiratory muscles, are therefore likely contribute more to pulmonary function (i.e. total respiratory pressure development and WOB) than the diaphragm in regards to generating the age-related augmented ventilatory response to meet the demands of the respiratory muscles during exercise in older adults (Smith et al., 2019).

In summary, research conducted by Smith and colleagues suggest that the higher respiratory muscle cost of exercise in older adults, due to increased ventilatory response and WOB, along with increased accessory respiratory muscle blood flow in older rats, may result in an earlier metaboreflex activation during high-intensity exercise in older adults compared to their younger counterparts.

2.4.5. Exercise-induced breathlessness

It is estimated that more than 30% of older adults aged >65 years’ experience breathlessness during daily activities (Guenette & Jensen, 2014; Ho et al., 2001; Tessier et al., 2001), with this symptom being generally accepted stoically as a natural component of the ageing process by sufferers (Morgan, Pendleton, Clague, & Horan, 1997). Consequently, dyspnoeic older adults often avoid physical activities which provoke the uncomfortable sensation of dyspnoea, leading to progressive cardiovascular and muscular deconditioning, and a downward spiral causing greater levels of dyspnoea during less strenuous activities (Guenette & Jensen, 2014).

Older adults report significantly greater dyspnoea than their younger counterparts at a given absolute exercise intensity (Killian, Summers, Jones, & Campbell, 1992; Mahler, Fierro-

Carrion, & Baird, 2003; Molgat-Seon et al., 2018a), and at a standardised submaximal $\dot{V}O_2$ (Ofir, Laveneziana, Webb, Lam, & O'Donnell, 2008). The reduced respiratory muscle strength in the older population, observed by Ofir et al. (2008), lead the authors to suggest that the respiratory muscle effort requirements in older adults represent a higher fraction of the maximal possible effort when exercising at the same metabolic load as younger adults. In this study, exertional dyspnoea and perceived leg discomfort correlated significantly with muscle strength measurements in all age groups, whereby dyspnoea increased as PI_{max} decreased, and perceived leg discomfort increased as leg strength decreased (Ofir et al., 2008). The increased levels of dyspnoea is likely related to an increased central motor command output with increased central corollary discharge to the somatosensory cortex (Chen, Eldridge, & Wagner, 1992; Gandevia & Macefield, 1989).

Ofir et al. (2008) also attributed the increased dyspnoea perception in older adults to the greater dynamic mechanical constraints, specifically the greater magnitude of expiratory flow limitation, increased V_T/IC, and reduced IRV compared to younger adults. A lower dynamic IRV at a given $\dot{V}O_2$ suggests higher operating position of V_T on the upper limits of the pressure-volume relationship of the respiratory system where increased elastic loading and functional weakness of the inspiratory muscles is observed (O'Donnell, Revill, & Webb, 2001; Ofir et al., 2008). More recently, Molgat-Seon et al. (2018a) proposed that WOB, breathing frequency, $\dot{V}_E/\dot{V}_{E\,CAP}$, and $\dot{V}_E$ were the strongest correlates of dyspnoea at an absolute exercise work rate of 80 W, and speculating that those with the highest indexes of mechanical constraint (WOB and $\dot{V}_E/V_{E\,CAP}$) experience greater sensations of dyspnoea. Interestingly, when mechanical ventilatory constraint was manipulated (WOB increased or decreased), dyspnoea remained unaffected in older men and women during short bouts of exercise at ventilatory threshold (Molgat-Seon et al., 2019). The authors suggested that as neuromechanical (un)coupling (the mismatch between respiratory motor output and the mechanical response to the output; Jensen et al., 2009) was experimentally manipulated in their study with no changes in dyspnoea perceptions, it is, therefore, not the main determinant of dyspnoea during exercise in older adults.

In summary, increased activity-related dyspnoea in older adults likely reflect the awareness of increased neural respiratory motor drive and contractile respiratory muscle effort, along with the accompanying increased central corollary discharge required to support a given ventilation during exercise (Guenette & Jensen, 2014). Furthermore, the multifactorial neurophysiological basis of exertional dyspnoea is unlikely to be explained by a single causative factor, and rather a combination of mechanisms, including reduced respiratory muscle strength, increased ventilatory constraints, and increased motor output of respiratory muscles (Gigliotti, 2010; Guenette & Jensen, 2014; Molgat-Seon et al., 2018a; Molgat-Seon et al., 2018b; Molgat-Seon et al., 2019; Ofir et al., 2008).

2.5. Inspiratory muscle training (IMT)

2.5.1. Overview and rationale of IMT

The aforementioned changes in the structure and function of the respiratory system in healthy older adults may result in an imbalance between the demand for respiratory muscle work and the capacity of these muscles to meet the demand. Thus, the rationale for IMT is to ameliorate this demand/capacity imbalance (McConnell, 2013), which in turn may result in reduced breathlessness (Moxham & Jolley, 2009).

Both strength and endurance training of the respiratory muscles can be implemented in a number of ways. A strength training stimulus can be applied via devices that impose resistance to the respiratory muscles at the mouth, whilst respiratory muscle endurance training can be achieved via prolonged periods of hyperventilation (McConnell, 2013). This thesis will primarily focus on inspiratory muscle strength training over endurance training due to the following considerations highlighted by McConnell (2013): 1) an individual's lack of endurance is usually secondary to their lack of strength, 2) the most effective way to ameliorate the demand/capacity imbalance of the respiratory muscles is to increase the strength and power of the respiratory pump, 3) strength training protocols elicit the greatest range of improvements in inspiratory muscle functional properties (i.e. strength, shortening velocity, power, and endurance), and 4) dyspnoea typically improves only if PI_{max} improves, which requires a strength-biased training protocol. Furthermore, as research has found that specific expiratory muscle training (EMT) and a combination of IMT and EMT is no more beneficial at increasing exercise capacity and reducing dyspnoea sensations than IMT alone (Griffiths & McConnell, 2007; Weiner, Magadle, Beckerman, Weiner, & Berar-Yanay, 2003), this thesis will focus on IMT only.

2.5.2. Methods of IMT

2.5.2.1. Flow resistive loading

Early studies, including Leith and Bradley (1976) sought to train the inspiratory muscles via flow resistive loading. This type of training involves inhalation via a variable diameter orifice, whereby, for a given flow, the smaller the orifice the greater the resistance (McConnell & Romer, 2004). Due to inspiratory pressure, and consequently training load, being dependent on flow rate, breathing pattern must be monitored during flow resistive loading in order to provide a quantifiable training stimulus (McConnell & Romer, 2004). A previous meta-analysis investigating the effects of respiratory muscle training in patients with COPD found that studies using flow resistive training failed to elicit improvements in inspiratory muscle function when inspiratory flow was not controlled (Smith, Cook, Guyatt, Madhavan, & Oxman, 1992).

2.5.2.2. Pressure-threshold loading

To train the inspiratory muscles using a pressure-threshold device, individuals must produce an inspiratory pressure sufficient to overcome a negative pressure load in order to initiate inhalation (McConnell & Romer, 2004). This type of training permits variable loading at a quantifiable intensity by providing near-flow-independent resistance to inspiration (Caine & McConnell, 2000). There are several ways in which pressure-threshold loading can be achieved, including, via a weighted plunger acting as an inspiratory valve (Nickerson & Keens, 1982), a solenoid valve (Bardsley et al., 1993), a constant negative pressure system (Chen, Que, & Yan, 1998), or a sprint-loaded poppet valve (Caine & McConnell, 2000). Due to its flow independence, IMT via pressure-threshold loading can be performed effectively without regulating breathing pattern (McConnell, 2013).

2.5.2.3. Tapered flow resistive loading (TFRL)

More recent developments in IMT devices have resulted in an electronic product which provides a tapered resistance via an electronic, dynamically adjusted valve allowing pressure to be volume-dependently tapered once an initial threshold has been overcome (Langer et al., 2015).

When a single inhalation performed during TFRL is compared to an inhalation during pressure-threshold loading by the same participant, TFRL resulted in more external work being performed (Langer et al., 2015). Once the initial threshold load is flow-independently overcome by the participant when training via TFRL, pressure is volume-dependently tapered. Due to the pressure-volume curve of the inspiratory muscles, the force that the inspiratory muscles can produce decreases with increasing lung volume (Rahn, Otis, Chadwick, & Fenn, 1946). Therefore, by reducing the absolute load during inhalation, TFRL accommodates the pressure-volume relationship and allows the resistance to be maintained at the same relative intensity throughout the inhalation (Langer et al., 2015). Participants training their inspiratory muscles via TFRL, therefore experience a “volume reward” for the effort required to produce the pressure corresponding to the initial threshold load, and allows V_{EI} to approach TLC, even at high intensities (Langer et al., 2015).

This, unfortunately, is not the case when training via threshold loading. Previous research has investigated the acute effects of pressure-threshold loading by recording cardiorespiratory variables whilst participants performed inspiratory loaded trials to the limit of tolerance at loads corresponding to 50, 60, 70, 80, and 90% PI_{max} (McConnell & Griffiths, 2010). Participants were instructed to maximise V_T throughout the loaded trials. The external work undertaken at intensities >60% PI_{max} was significantly reduced, with the authors attributing this to the significant decrease in V_T over time at 60, 70, 80% PI_{max} and consequently the premature termination of the trials (McConnell & Griffiths, 2010). This is likely due to the constant pressure throughout inspiration in these types of devices, whereas TFRL provides a training stimulus to the inspiratory muscle at shorter lengths (similar to operating lengths observed during exercise; Langer et al., 2015).

Langer et al. (2015) also compared the chronic effects of a short home-based IMT programme in COPD who used either a TFRL device or a pressure-threshold device. Both groups of patients were required to perform two daily sessions of 30 breaths at around 50% PI_{max} for 8 weeks. It was found that, during the last 3 weeks of training, the TFRL groups tolerated greater training loads than the pressure-threshold group with similar effort scores reported between groups. Following training, the TFRL group achieved significantly higher improvements in inspiratory muscle strength, power, shortening velocity, and endurance than the pressure-threshold group.

2.5.3. Responses during acute inspiratory muscle loading

Previous studies have sought to determine the acute physiological responses to inspiratory muscle loading (da Fonsêca, Resqueti, Benício, Fregonezi, & Aliverti, 2019; de Souza et al., 2016; McConnell & Griffiths, 2010; Ross, Nowicky, & McConnell, 2007). McConnell and Griffiths (2010) reported that inspiratory loading at 60% PI_{max} resulted in the greatest external work (the product of the pressure load and the volume change achieved at that load). Higher loads (80% PI_{max}) resulted in the lowest external work due to the direct effect of lower V_T at higher intensities, which may question the efficacy of high-intensity IMT protocols and their influence on inspiratory muscle function (McConnell & Griffiths, 2010).

Non-invasive measurements of chest wall volumes (i.e. OEP), have been utilised by researchers to investigate respiratory pattern and thoracoabdominal compartmental distribution during incremental (Da Gama et al., 2013), pressure-threshold (Brandão et al., 2012; de Souza et al., 2016), and TFRL (da Fonsêca et al., 2019). In particular relevance to this thesis, de Souza et al. (2016) investigated the age-related differences in thoracoabdominal volume responses to inspiratory pressure-threshold loading between a group of healthy older women (average age: 68.2 years) and younger women (average age: 23.9 years). The authors assessed variables of total and compartmental V_T and percentage contribution of thoracoabdominal compartments (pulmonary rib cage, RCp; abdominal rib cage, RCa; and abdomen, Ab) during 3 minutes of QB, 3 minutes of moderate inspiratory resistance (40% PI_{max}), and during 2 PI_{max} manoeuvres. During QB, the predominant compartment was Ab within the older group, whereas in younger individuals, the predominant compartment was RCp, likely explained by the age-related structural and physiological changes of the respiratory system mentioned previously. During moderate inspiratory resistance, contribution of the Ab and RCp compartments were similar in the older group with RCp remaining the predominant compartment in the younger group. Finally, during PI_{max} manoeuvres, both age groups showed a similar response in chest wall volume distribution with the RCp compartment having the greatest contribution. The altered volume distribution within the older group was explained by the decrease chest wall compliance, with moderate inspiratory resistance being insufficient to overcome the resistive forces of the upper chest wall (de Souza et al., 2016).

The acute thoracoabdominal volume responses to TFRL have also been assessed via OEP (da Fonsêca et al., 2019). The authors observed significant increases in V_T during inspiratory loading at 20% and 40% PI_{max} which was attributed to significant increases in V_{EI} and decreases in V_{EE}. Increased V_{EI} was due to increased (RCp and RCa compartments) volumes, highlighting the importance of rib cage muscles in increasing V_T expansion (da Fonsêca et al., 2019). Decreased V_{EE} was due to a decreased V_{EE} within the AB compartment only, which supports diaphragmatic contraction by increasing the pre-inspiratory length of the diaphragm and preventing excessive shortening (Aliverti et al., 1997; da Fonsêca et al., 2019).

2.5.4. Adaptations and responses to IMT

Specific details regarding the literature surrounding the effects of IMT in healthy older adults will be outlined and discussed in chapter 3 via a systematic review and meta-analysis. This section, however, will provide a brief summary of the benefits of IMT in healthy and diseased populations.

2.5.4.1. Structural and functional adaptations following IMT

In terms of structural adaptations, 5 weeks of pressure-threshold IMT has been shown to increase the proportion of fatigue-resistant type I muscle fibres by 38%, along with increase the cross-sectional area of type II muscle fibres by 21% of the external intercostal muscle in COPD patients (Ramírez-Sarmiento et al., 2002). Furthermore, significant increases in diaphragm thickness following an IMT programme have been observed in healthy young (Downey et al., 2007; Enright, Unnithan, Heward, Withnall, & Davies, 2006) and older individuals (Souza et al., 2014), as well as those with chronic heart failure (CHF; Chiappa et al., 2008), cystic fibrosis (Enright, Chatham, Ionescu, Unnithan, & Shale, 2004), and stroke (Cho, Lee, Kim, & Lee, 2018).

The functional adaptations of IMT include increased strength, contraction speed, power output and/or endurance of the inspiratory muscles (McConnell, 2013). As with skeletal muscles, inspiratory muscles follow the general principle of force-velocity (pressure-flow) specificity of training, in that high-pressure training elicits improvements in strength (increased PI_{max}) , and training with high-flow elicits improvements in speed of contraction (increased peak inspiratory flow rate; Romer & McConnell, 2003). Training stimuli with intermediate pressure (~60% PI_{max}) allowing for moderate flow rates have been shown to elicit improvements in both strength and speed (and consequently power output) of the inspiratory muscles (Romer & McConnell, 2003; Tzelepis et al., 1994). This optimal moderate-pressure and flow training can typically be sustained for ~30 breaths, with this protocol also proven to elicit significant improvements in endurance in healthy individuals (Caine & McConnell, 1998).

A number of systematic reviews and meta-analyses have suggested that IMT can improve PI_{max}, peak inspiratory flow rate, and respiratory muscle endurance in healthy individuals (HajGhanbari et al., 2013; Illi et al., 2012), as well as patients with COPD (Beaumont et al., 2018; Geddes et al., 2008), and CHF (Smart et al., 2013).

2.5.4.2. Exercise/functional capacity following IMT

Exercise to the limit of tolerance post-IMT is increased in healthy individuals (Bailey et al., 2010; Caine & McConnell, 1998; Edwards & Cooke, 2004; Gething, Williams, & Davies, 2004; Illi et al., 2012; Johnson, Sharpe, & Brown, 2007), with improvements ranging from ~5–30%. Furthermore, evidence suggests that IMT can also increase time trial performance in this population (Illi et al., 2012; Johnson et al., 2007; Romer et al., 2002a; Volianitis et al., 2001), albeit with only slight improvements observed (~2–5%). As for those suffering from clinical conditions, various meta-analyses have shown IMT to be effective in improving exercise capacity (usually assessed via walk tests such as the six-minute walk test; 6MWT) in COPD (Beaumont et al., 2018; Geddes et al., 2008; Gosselink et al., 2011), CHF

(Montemezzo, Fregonezi, Pereira, Britto, & Reid, 2014; Smart et al., 2013; Wu, Kuang, & Fu, 2018), and post-stroke patients (Gomes-Neto et al., 2016).

2.5.5. Potential underpinning mechanisms of improved exercise capacity

An improved exercise capacity following IMT has been attributed to various physiological mechanisms, including, reduced respiratory muscle fatigue, improved respiratory muscle efficiency, reduced effort perception, attenuated respiratory muscle metaboreflex, reduced blood lactate $[La^-]_B$ concentrations, and improved ventilatory parameters.

2.5.5.1. Reduced respiratory muscle fatigue

One potential mechanism of increased exercise capacity following IMT may be reduced respiratory muscle fatigue. Previous studies have observed diminished post-exercise inspiratory muscle fatigue levels, measured via PI_{max}, following an IMT programme (Bailey et al., 2010; Romer et al., 2002c; Volianitis et al., 2001). Within these studies, post-exercise PI_{max} values were observed to be within 3–9% of pre-exercise values after IMT compared with an 11–23% reduction before IMT. Furthermore, PI_{max} values measured 10-minutes following severe intensity exercise were not significantly different to pre-exercise values following IMT but remained significantly reduced in the SHAM-IMT control group, implying a more rapid recovery time for the inspiratory muscles after IMT compared with the control (Bailey et al., 2010).

As the fatigability of the respiratory muscle is, to a certain extent, governed by their baseline strength (McConnell, Caine, & Sharpe, 1997; Romer et al., 2002c), a strength training stimulus which specifically targets the inspiratory muscles is expected to reduce inspiratory muscle fatigue. Some studies, however, have not observed attenuated respiratory muscle fatigue following IMT even in the presence of improved inspiratory muscle strength and exercise capacity (Griffiths & McConnell, 2007; Johnson et al., 2007). Possible explanations for this include: 1) the inability of PI_{max} measurements to discriminate either fatigue between various inspiratory muscles or between peripheral and central components of fatigue (Johnson et al., 2007), 2) the attenuation of inspiratory muscle fatigue per se not playing a role in improving exercise capacity (Griffiths & McConnell, 2007), and 3) inspiratory muscle fatigue may have been delayed but not attenuated, allowing for limb blood flow to be maintained for longer during exercise following IMT (Griffiths & McConnell, 2007).

In the studies that did observe an IMT-mediated attenuation of inspiratory muscle fatigue following high-intensity exercise, this may be related to the aforementioned structural and functional adaptations following training. Specifically, increased diaphragm thickness (Downey et al., 2007; Enright et al., 2006; Souza et al., 2014) and increased proportion of fatigue-resistant type I muscle fibres (Ramírez-Sarmiento et al., 2002) which may contribute to increase respiratory muscle oxidative capacity and reduce the oxygen cost of breathing at a given work rate (Turner et al., 2012).

2.5.5.2. Improved respiratory muscle efficiency

Following an IMT programme consisting of 30 repetitions at 50% PI_{max}, twice daily for 6 weeks, Turner et al. (2012) found that the O_2 cost of breathing ($\dot{V}O_{2RM}$) was significantly reduced at high levels of $\dot{V}_E$ in trained cyclists. The participants performed three separate bouts of eucapnic voluntary hyperpnoea (EVH) matching $\dot{V}_E$ at 50, 75, and 100% $\dot{V}O_{2\,max}$ both pre- and post-IMT. A curvilinear relationship was observed between $\dot{V}O_{2RM}$ and $\dot{V}_E$, whereby, at higher levels of $\dot{V}_E$, the increase in $\dot{V}_E$ was disproportionate to the increase in $\dot{V}O_{2RM}$. The authors suggested that this could be attributed to various factors of respiratory work, including increased elastic recoil of the lung and chest wall, increased airway resistance, higher muscle shortening velocities, and/or increased V_{EE} (Turner et al., 2012). The $\dot{V}O_{2RM}$ during EVH pre-IMT ranged from between ~4% of total $\dot{V}O_2$ ($\dot{V}O_{2T}$) at low-intensity exercise and ~11% of

$\dot{V}O_{2T}$ at maximal intensity exercise. This finding supports previous research suggesting that the respiratory muscles require around 10–15% of $\dot{V}O_{2T}$ during maximal exercise (Aaron et al., 1992; Harms et al., 1998).

The 6-week IMT programme resulted in significantly reduced $\dot{V}O_{2RM}$ from pre-IMT values at both maximal and submaximal levels of $\dot{V}_E$ (Turner et al., 2012). Post-IMT $\dot{V}O_{2RM}$ (as a percentage of $\dot{V}O_{2T}$) was reduced by 1.5% at a $\dot{V}_E$ corresponding to 75% $\dot{V}O_{2\,max}$, and by 3.4% at a $\dot{V}_E$ corresponding to 100% $\dot{V}O_{2\,max}$, suggesting that this reduction in O_2 requirement of the respiratory muscles, and therefore, increased efficiency of the respiratory pump at a given ventilation, may facilitate an increased O_2 availability to the active locomotor muscles during exercise (Turner et al., 2012). The authors attributed the reduced $\dot{V}O_{2RM}$ to the 22% increase in PI_{max}, and the potential associated increased cross-sectional area of inspiratory muscle fibres observed previously (Ramírez-Sarmiento et al., 2002). This increased inspiratory muscle strength may result in the recruitment of fewer muscle fibres and/or delay the recruitment of accessory respiratory muscles, for a given $\dot{V}_E$, and subsequently reduce the O_2 cost of EVH (Turner et al., 2012). Furthermore, an improved respiratory muscle efficiency may also explain IMT-mediated reductions in heart during equivalent exercise intensities which has been observed in some (Gething et al., 2004; Griffiths & McConnell, 2007) but not all (Bailey et al., 2010; Enright et al., 2006) studies.

2.5.5.3. Reduced respiratory and locomotor muscle effort perception

A decreased perceived respiratory effort during exercise following IMT has been observed in healthy individuals (Bailey et al., 2010; Griffiths & McConnell, 2007; Ramsook et al., 2017; Romer et al., 2002a, 2002b; Volianitis et al., 2001) and diseased populations (Charususin et al., 2018; Langer et al., 2018; Shahin, Germain, Kazem, & Annat, 2008; Weiner, Magadle, Berar-Yanay, & Pelled, 1999).

The reduced respiratory effort perceptions following IMT is likely due to improvements in contractile properties of the inspiratory muscles (Kellerman, Martin, & Davenport, 2000; Romer et al., 2002a). Specifically, the increased force-generating capacity of these muscles following training decreases the relative tension for a given ventilation, and consequently reduces the perceived intensity of respiratory effort during exercise (Romer et al., 2002a).

In COPD patients, the IMT-induced reductions in respiratory effort during exercise may be explained by a reduced diaphragm activation (EMGdi) when expressed relative to its maximum ($\text{EMGdi}/\text{EMGdi}_{\text{max}}$; Langer et al., 2018). This finding occurred due to an increased $\text{EMGdi}_{\text{max}}$, obtained during maximal IC manoeuvres, following IMT, due to strength and neural adaptations, facilitating an increased ability to recruit more motor units during maximal voluntary contraction of the diaphragm (Häkkinen et al., 1998; Langer et al., 2018). Less motor unit recruitment during tidal EMGdi was therefore required to generate a given force due to muscle hypertrophy (Häkkinen et al., 1998; Ramírez-Sarmiento et al., 2002), reducing the proportion of maximal motor command output signals to the diaphragm required to sustain $\dot{V}_{\text{E}}$ (Langer et al., 2018).

This finding has been supported by Huang et al. (2003), who found that increased PI_{max} following 4 weeks of IMT was associated with a reduced inspiratory motor command (assessed via mouth occlusion pressure at 0.1 s; $\text{P}_{0.1}$). A recent study conducted by Ramsook et al. (2017), however, argues that IMT does not affect neural respiratory drive, and that improvements in exertional dyspnoea following training are not explained by improvements in key physiological outcomes (i.e. electrical activity of the inspiratory muscles, ventilatory responses, and neuromechanical coupling of the respiratory system) contributing to dyspnoea in healthy and diseased populations. It is clear at the present time that the mechanisms behind IMT-induced reductions in perceived respiratory effort remains inconclusive and requires further investigation in various populations.

Research has also provided evidence of reduced perceived locomotor muscle effort following IMT (Bailey et al., 2010; Romer et al., 2002a, 2002b). The physiological mechanisms underlying this IMT-induced response are likely to be related to the attenuation of the inspiratory muscle metaboreflex ameliorating the competition for blood flow between respiratory and locomotor muscles (McConnell & Lomax, 2006; Witt et al., 2007), along with reductions in $[La^-]_B$ concentrations (Bailey et al., 2010; Brown, Sharpe, & Johnson, 2008; Romer et al., 2002b).

2.5.5.4. Reduced blood lactate concentrations

An attenuated $[La^-]_B$ response to exercise has also been observed following IMT (McConnell & Sharpe, 2005; Romer et al., 2002b; Volianitis et al., 2001). During submaximal endurance exercise, Romer et al. (2002b) observed significantly lower $[La^-]_B$ response following a 6-week IMT programme, and stated that changes in inspiratory muscle function were related to the attenuated metabolic response, as changes in PI_{max} accounted for ~59% of the variance in $[La^-]_B$. Furthermore, McConnell and Sharpe (2005) reported a significant reduction in $[La^-]_B$ at maximum lactate steady state (MLSS) during constant work rate (CWR) exercise. The authors did not observe any change in MLSS power and therefore concluded that the reductions in $[La^-]_B$ concentrations were not attribute to a substantial increase in the lactate threshold.

IMT has also been reported to attenuate increases in $[La^-]_B$ following volitional hyperpnoea (Brown et al., 2008). The authors observed that 10 minutes of volitional hyperpnoea approximately doubled resting $[La^-]_B$, and a 6-week IMT programme attenuated this increase by 25%. The increase in $[La^-]_B$ was concluded to be a result of increased lactate efflux from the respiratory muscles as opposed to respiratory alkalosis. IMT-mediated reductions in $[La^-]_B$ during relatively low $\dot{V}_E$ have been suggested to be as a result of increased uptake and metabolism of lactate by trained respiratory muscles (Brown et al., 2008; Griffiths & McConnell, 2007; Spengler, Roos, Laube, & Boutellier, 1999).

2.5.5.5. Attenuation of the inspiratory muscle metaboreflex

Research has shown that IMT can attenuate the inspiratory muscle metaboreflex by increasing the intensity of inspiratory muscle work required to activate this reflex (Chiappa et al., 2008; McConnell & Lomax, 2006; Witt et al., 2007). McConnell and Lomax (2006) aimed to determine whether prior inspiratory muscle fatigue would influence the rate of fatigue development during plantar flexor exercise, and whether a 4-week IMT programme would ameliorate this influence. Prior fatigue of the inspiratory muscles was induced via acute inspiratory loading at 60% PI_{max} with a constant breathing frequency of 15 breaths/minute, and V_T of 1.5 L, until participants failed to maintain the target pressure (as based upon previous methods; Sheel et al., 2001). The authors found inspiratory muscle fatigue accelerated plantar flexor fatigue compared to the control trial of plantar flexor exercise with no prior inspiratory fatigue. This inspiratory fatigue-induced reduction in plantar flexor exercise performance was observed to be similar to when limb blood flow was mechanically restricted via a thigh cuff inflated to 140 mmHg (McConnell & Lomax, 2006).

Following a 4-week IMT programme consisting of 30 breaths, twice daily at 50% PI_{max}, participants repeated the previous fatiguing protocols at both the same absolute intensity, and the same relative intensity, taking into account the IMT-induced improvements in PI_{max}. IMT significantly improved the plantar flexor exercise time to the limit of tolerance following the resistive breathing task at the same absolute intensity as pre-IMT but not the same relative intensity (McConnell & Lomax, 2006), suggesting that IMT improves limb vascular conductance during inspiratory loading and attenuates the inspiratory muscle metaboreflex.

Witt et al. (2007) have also reported an attenuated metaboreflex response following a 5-week IMT programme. Prior to training, participants performed a resistive breathing task designed to induce the inspiratory muscle metaboreflex, similar to previous studies (McConnell & Lomax, 2006; Sheel et al., 2001), which was confirmed by an observed time-dependent rise in heart rate and MAP (Witt et al., 2007). During the post-intervention resistive breathing task, performed at the same absolute intensity as pre-intervention, the IMT group showed a blunted heart rate response and a nearly abolished MAP response, compared to no significant differences in responses observed between pre- and post-training tests in the control, SHAM-IMT group (Witt et al., 2007). The authors suggest that the attenuated metaboreflex may relate to various underlying mechanisms such as less mechanoreceptor activity during the post-IMT resistive breathing task due to a reduced responsiveness to a given mechanical stimulus, and the conditioning of type III receptors during IMT (Witt et al., 2007). Alternative mechanisms may also include an improved aerobic capacity of the respiratory muscles, reducing the imbalance between diaphragmatic blood flow and metabolic demand and/or decreased responsiveness of the chemoreceptors to a given metabolic stimulus due to repeated metabolite exposure during IMT (Witt et al., 2007).

Similar findings of an attenuated inspiratory muscle metaboreflex response have been observed in CHF patients (Chiappa et al., 2008; Moreno et al., 2017). Specifically, IMT improved blood flow to resting calf muscles during fatiguing inspiratory loading and to exercising forearm muscles during handgrip exercises following inspiratory muscle fatigue (Chiappa et al., 2008), and attenuated intercostal and forearm muscle oxygen demand-delivery mismatch during fatiguing inspiratory contractions (Moreno et al., 2017).

2.5.5.6. Improved $\dot{V}$O2 kinetics and ventilatory parameters

An improved blood flow to exercising muscles and absence of the inspiratory muscle metaboreflex has been suggested as the mechanisms behind improved $\dot{V}O_2$ kinetics during exercise following IMT (Bailey et al., 2010; Brown, Sharpe, & Johnson, 2012).

Four weeks of pressure-threshold IMT significantly reduced the $\dot{V}O_2$ slow component during severe and maximal intensity exercise in healthy individuals (Bailey et al., 2010). These findings have been confirmed by Brown et al. (2012), who also observed a reduced phase II time constant following 6 weeks of IMT. The authors suggested that this was due to increased inspiratory muscle oxidative capacity (increased intracellular oxygen utilisation) resulting in reduced metabolic inertia, potentially due to increased type I muscle fibres following IMT (Brown et al., 2012).

In COPD patients with inspiratory muscle weakness, the addition of IMT to a pulmonary rehabilitation programme resulted in significantly greater V_T and slower breathing frequency during exercise at 80% and 100% baseline peak $\dot{V}_E$ (Charususin et al., 2016). These changes were not accompanied by significant changes in inspiratory flow rates following training which have been observed in previously (Petrovic et al., 2012). This increased V_T and decreased breathing frequency has also been reported following respiratory muscle endurance training (Koppers, Vos, Boot, & Folgering, 2006), with the authors stating the advantages of this breathing pattern being: 1) decreased ratio of dead space to V_T, leading to an increase in effective alveolar ventilation, 2) diminished WOB (Nici, 2000), and 3) delayed respiratory muscle fatigue, which would prevent a rapid, shallow breathing pattern being adopted (Larson & Kim, 1987).

Charususin and colleagues were unable to identify whether the greater V_T was as a result of increased V_{EI} (reduced mechanical restriction on V_T expansion) or decreased V_{EE} (reduced dynamic hyperinflation; Charususin et al., 2016). It was suggested that, as inspiratory time (T_I) increased in proportion to expiratory time (T_E) and the ratio of T_I to total breath duration (T_{TOT}; T_I/ T_{TOT}) remained constant, it is likely that the increase in V_T was a result of increased V_{EI}, however, the authors highlighted the importance of more elaborate measurement techniques to determine the effects of IMT on operating lung volumes (Charususin et al., 2016).

Conversely, Petrovic et al. (2012) observed a reduction in dynamic hyperinflation (reflected by significantly increased inspiratory fraction) during exercise in COPD patients following 8 weeks of IMT. The authors attributed this to enhanced velocity of inspiratory muscle shortening and decreased T_I, leading to greater T_E facilitating lung emptying (Petrovic et al., 2012). As with Charususin et al. (2016), Petrovic et al. (2012) reported an improved breathing pattern following IMT, reflected by a decreased breathing frequency to $\dot{V}_E$ ratio. Other studies have reported no significant changes in breathing pattern or operating lung volumes following IMT in COPD (Langer et al., 2018) and healthy individuals (Ramsook et al., 2017).

Recent studies have utilised OEP to further investigate the effects of IMT on breathing patterns and operating thoracoabdominal volume regulation (Hoffman et al., 2021; Medeiros et al., 2019). Medeiros et al. (2019) observed a significant increase of 0.1 L in the RCp volume of chronic kidney disease patients during IC manoeuvres following IMT compared to the control group. No difference, however, was observed during QB between groups. Hoffman et al. (2021) also reported no significant changes in breathing pattern or thoracoabdominal volume regulation in advanced lung disease patients. The authors stated that the main limitation of this study was the lack of OEP measurements during exercise, and suggested that IMT may only elicit changes in breathing pattern during when the respiratory system is placed under higher demands during exercise.

2.6. Study aims

As this literature review has outlined, the healthy ageing process can cause significant alterations in the respiratory system which may consequently lead to exercise intolerance. The purpose of this thesis is to review the existing literature on the effects of IMT in healthy older adults before investigating the acute and chronic effects of IMT in this population. The experimental chapters within this thesis will specifically focus on utilising OEP techniques to determine thoracoabdominal volume regulation both during acute inspiratory loading, and during exercise following an IMT intervention.

Study 1 (Chapter 3): Inspiratory muscle training for improving inspiratory muscle strength and functional capacity in older adults: a systematic review and meta-analysis

To systematically review and perform a meta-analysis on the effects of IMT for improving inspiratory muscle strength and functional capacity in healthy older adults, and to determine, if any, the association between baseline PI_{max} and change in PI_{max} following IMT within included studies.

Study 2 (Chapter 5): Acute thoracoabdominal volume responses to tapered flow resistive loading in younger and older adults

To investigate the effects of age on thoracoabdominal volume regulation, gas exchange responses and ratings of breathlessness between TFRL at low, moderate, and high intensities in younger and older adults. A secondary aim of this chapter was to investigate whether maximising V_T and reducing breathing frequency during TFRL reduces sensations of breathlessness and hypocapnia.

Study 3 (Chapter 6): The effects of inspiratory muscle training on thoracoabdominal volume regulation healthy older adults

To determine whether an 8-week IMT intervention improves respiratory muscle strength and exercise tolerance in healthy older adults, and to investigate whether changes in thoracoabdominal volume regulation are observed during exercise following IMT. Secondary aims of this chapter were to investigate whether IMT improves physical activity levels, balance, and quality of life.

Study 4 (Chapter 7): Older adults’ perspectives and views on inspiratory muscle training: a qualitative perspective

To explore older adults’ perspectives and views towards IMT both immediately following the 8-week IMT intervention in chapter 6 and at 3-months post training.

CHAPTER 3 - INSPIRATORY MUSCLE TRAINING FOR IMPROVING INSPIRATORY MUSCLE STRENGTH AND FUNCTIONAL CAPACITY IN OLDER ADULTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

3.1. Introduction

3.1.1. Background

As outlined in chapter 2, previous meta-analyses have suggested that IMT can improve inspiratory muscle strength (reflected by an increase in PI_{max}), six-minute walking distance (6MWD) and quality of life in COPD (Geddes et al., 2008; Gosselink et al., 2011) and CHF patients (Smart et al., 2013). Reduced inspiratory muscle strength is not only associated with COPD (Gosselink, Troosters, & Decramer, 2000) and CHF patients (Ambrosino et al., 1994), but is also characteristic of the ageing process (Pegorari et al., 2013), with several studies in healthy older adults (Albuquerque, Rossoni, Cardoso, Paiva, & Fregonezi, 2013; Aznar-Lain et al., 2007; Huang, Yang, Wu, & Lee, 2011; Kaneko, Suzuki, & Horie, 2022) reporting PI_{max} values as low as those reported in patients with lung or heart disease (Dall'Ago, Chiappa, Guths, Stein, & Ribeiro, 2006; Hill et al., 2006; Huang et al., 2011). Respiratory muscle performance in older adults is impaired due to increased RV and FRC during the ageing process, which consequently increases WOB and associated breathlessness during activities of daily living in this population (Janssens, 2005). Therefore, exertional breathlessness in older adults may compromise an individual's daily functional capacity and quality of life (Ho et al., 2001).

Due to the age-related decline in respiratory muscle function, it is likely that IMT will also have a beneficial effect in older adults without a long-term condition given that in this population, reduced respiratory muscle strength is associated with a decline in pulmonary function (Buchman et al., 2008a), mobility (Buchman et al., 2008a; Buchman et al., 2008b), reduced physical performance (Watsford et al., 2007), and constitutes an independent risk factor for myocardial infarction and cardiovascular mortality (Van der Palen et al., 2004). Thus, interventions that increase respiratory muscle function may have an important clinical impact in healthy older adults.

3.1.2. Review objective

To systematically review and perform a meta-analysis on the effects of IMT for improving inspiratory muscle strength and functional capacity in healthy older adults.

3.2. Methods

3.2.1. Search strategy

This prospectively registered systematic review (CRD42019155163; https://www.crd.york.ac.uk/prospero/) followed the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009). Electronic databases (Medline/PubMed, Cochrane Library, Web of Science and CINAHL) were searched from August 2019 to February 2020. Databases were searched again in March 2022 to identify records published between February 2020 and March 2022.

The final search strategy included relevant MeSH Terms, Text Words and Publication Types relating to the population (e.g. “aged” and “older adults”), the intervention (e.g. “inspiratory muscle training” and “breathing exercises”), the outcomes (e.g. “exercise tolerance”, “quality of life” and “maxim* inspiratory”) and the design (e.g. “random*”, “clinical trial” and “experimental study”). These terms were constructed and grouped by Boolean logic with no restrictions on publication date. The full PubMed search strategy is outlined in Table 3-1

Table 3-1. Search strategy for literature search conducted in PubMed.

Search	Query
#1	(“Aged”[MeSH Terms] OR “aged, 80 and over”[MeSH Terms] OR “middle aged”[MeSH Terms] OR “aged/physiology”[MeSH Terms] OR “older adults”[Text Word] OR “elderly”[Text Word] OR “Frail elderly”[MeSH Terms] OR “frail”[Text Word] OR “frailty”[Text Word] OR “inspiratory muscle weakness”[Text Word]).
#2	(“Breathing exercises”[MeSH Terms] OR “breathing exercises/methods”[MeSH Terms] OR “inhalation”[MeSH Terms] OR “inhalation/physiology”[MeSH Terms] OR “inspiratory muscle training”[Text Word] OR “inspiratory muscle strength training”[Text Word] OR “respiratory muscle training”[Text Word] OR “inspiratory threshold training”[Text Word] OR “ventilatory muscle training”[Text Word]).
#3	(“Respiratory muscles”[MeSH Terms] OR “respiratory muscles/physiology”[MeSH Terms] OR “respiratory muscles/physiopathology”[MeSH Terms] OR “exercise tolerance”[MeSH Terms] OR “respiratory function test”[MeSH Terms] OR “quality of life”[MeSH Terms] OR “maximal respiratory pressures”[MeSH Terms] OR “maxim* inspiratory”[Text Word] OR “functional capacity”[Text Word] OR “exercise capacity”[Text Word] OR “exercise tolerance”[Text Word] OR “quality of life”[Text Word]
#4	(“Randomized Controlled Trial”[Publication Type] OR “Multicenter Study”[Publication Type] OR “Clinical Trial”[Publication Type] OR “Comparative Study”[Publication Type] OR “random*”[Text Word] OR “experimental study”[Text Word] OR “clinical trial”[Text Word]).
#5	#1 AND #2 AND #3 AND #4.

3.2.2. Inclusion and exclusion criteria

MeSH Terms/Text Words including “frail elderly”, “frail” and “frailty” were included in the search strategy due to the finding that, during pre-scoping, these keywords were associated with older populations with weaker inspiratory muscles undertaking IMT programmes (Ferraro, Gavin, Wainwright, & McConnell, 2019). The MeSH Term “breathing exercises” was also included as, during pre-scoping, it was found to be associated with IMT in some studies (Ferraro et al., 2019; Huang et al., 2011; Mills, Johnson, Barnett, Smith, & Sharpe, 2015; Watsford & Murphy, 2008). Studies were considered eligible if they fulfilled the pre-determined participants, interventions, comparisons and outcomes (PICOS) criteria (Table 3-2).

Initial screening of titles and abstracts and assessment of full texts were performed independently by two reviewers who were blinded to each other’s decisions. Any disagreements between the authors were sent to a third reviewer to settle the disagreement.

Table 3-2. Inclusion and exclusion criteria.

	Inclusion	Exclusion
Population	Healthy older adults (>60)	Individuals <60 years. Populations with medical conditions that could affect the magnitude of improvement in PI_{max} (i.e., COPD, CHF, frailty)
Intervention	Inspiratory muscle resistance training via resistive or threshold loading	Inspiratory muscle endurance training (i.e., isocapnic hyperpnoea training)
Comparison	Participants receiving no intervention, SHAM IMT or low versus high intensities of IMT	Studies not utilising any comparison groups were excluded
Outcomes	Inspiratory muscle strength, functional or exercise capacity and quality of life	Studies that did not include at least one of the outcomes listed in the inclusion section were excluded
Studies	Randomised and non-randomised controlled trials	Animal/non-human studies were excluded

3.2.3. Data extraction

Data was extracted in terms of the following subheadings. 1) author information (first author and year of publication), 2) participant characteristics (age, gender, baseline PI_{max}), 3) mode of IMT and supervision, 4) time, intensity and progression of IMT, 5) frequency and duration of IMT, 6) control and 7) outcomes assessed.

3.2.4. Quality assessment

The PEDro quality scale was used to assess internal and external validity of the included studies (Maher, Sherrington, Herbert, Moseley, & Elkins, 2003). Two authors independently reviewed each included study on the following domains of the PEDro scale: eligibility criteria, random allocation, concealed allocation, baseline similarity, blinding of subjects, therapist and assessor, measures obtained from more than 85% of subjects initially allocated to groups, full intention to treat, group comparison, and point measures and measures of variability. PEDro scale scores 9–11 were considered excellent, 6–8 good, 4–5 fair and ≤3 poor (Maher et al., 2003). No study was excluded based on poor quality.

3.2.5. Data analysis

Meta-analyses of the studies were performed using the software Review Manager (RevMan V5.3; Cochrane Collaboration, Oxford, UK). Outcomes were continuous and change scores with standard deviations were used to obtain effect size reported as standard mean differences with 95% confidence intervals. The heterogeneity of studies were assessed by the I^2 value, and were classified as might not be important (0–40%), moderate heterogeneity (30–60%), substantial heterogeneity (50–90%), and considerable heterogeneity (75–100%; Higgins & Green, 2011). A small minimum clinically important difference (MCID) in functional capacity was observed if participants in the IMT groups improved their 6MWD by above 20 m and a substantial MCID if the improvement was over 50 m (Perera, Mody, Woodman, & Studenski, 2006). A random-effects model was used for the meta-analyses as variation in methods were found between included studies beyond random sampling. Pearson's correlation analysis was performed in order to determine the association between baseline PI_{max} and change in PI_{max} following IMT within included studies. The level of significance for all analyses was set at $p<0.05$.

3.3. Results

The databases yielded 986 studies (Figure 3-1). Following the removal of 181 duplicates and screening of 805 titles/abstracts, 19 articles remained for full-text screening of which 11 were excluded. A further 5 studies published between the initial database search and March 2022 were identified during subsequent database searching and screening. Overall, 13 studies were included in this systematic review (Table 3-3) with one of these studies (Albuquerque et al., 2013) excluded from the meta-analysis due to insufficient data reported (Table 3-3). Furthermore, due to 2 papers (Rodrigues, Dal Lago, & da Silva Soares, 2021a; Rodrigues, Gurgel, Galdino, da Nóbrega, & Soares, 2020) arising from one large study consisting of similar participants, and thus similar mean change scores for PI_{max}, only the most recently published paper (Rodrigues et al., 2021a) was included within the meta-analysis.

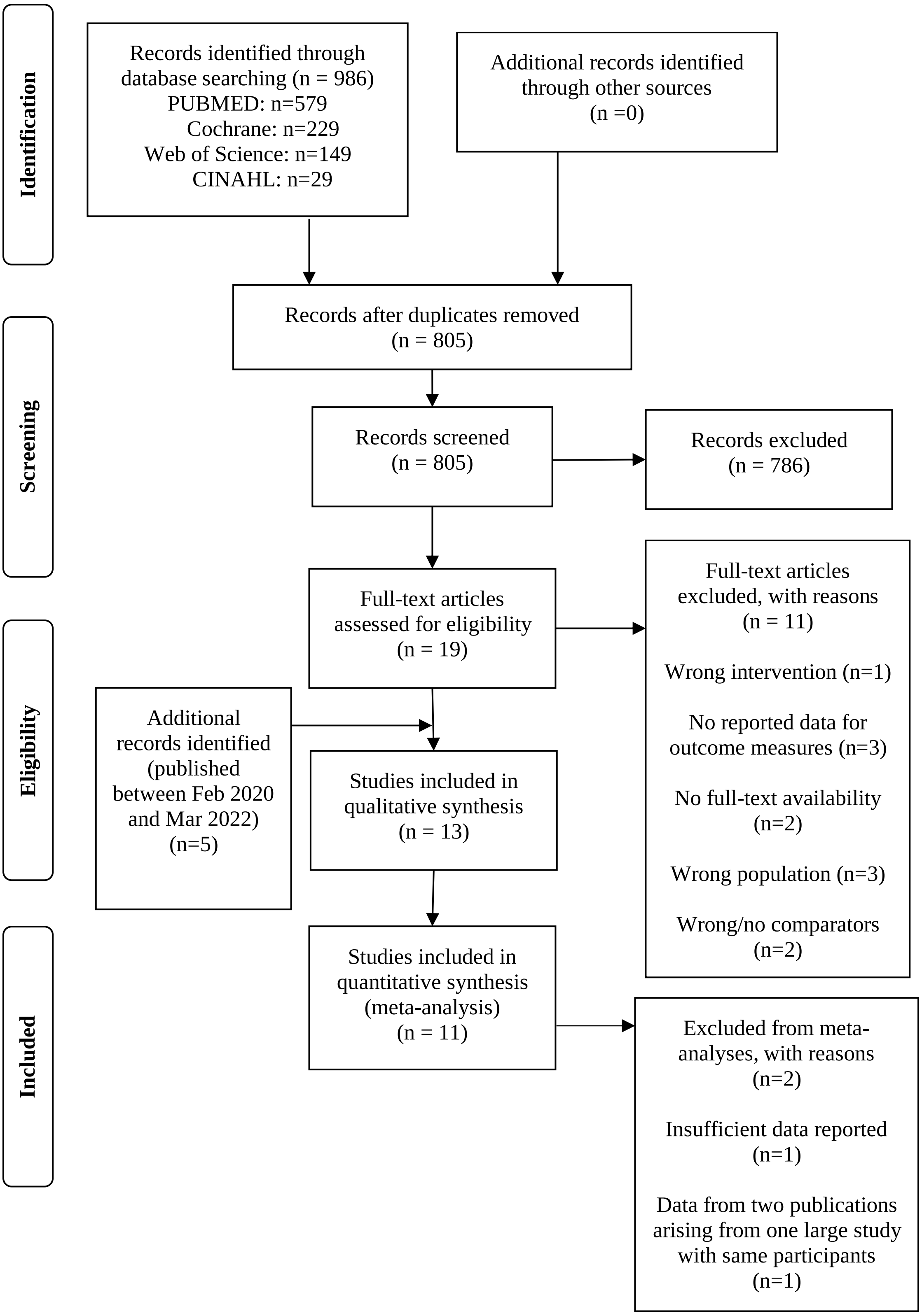


Figure 3-1. PRISMA flow diagram of studies through database search and selection process; n=number.

Table 3-3. Characteristics of included studies.

Author	Year	N (I/C)	Age, years; mean (SD)	Gender (M/F)	Baseline PI_{max} (cmH_2O)	Mode of IMT and supervision	Time, intensity and progression of IMT	Frequency and duration of IMT	Control	Outcomes assessed
Albuquerque et al. (2013)	2013	13/13	IMT: 68.5 (64.7–76) CG: 67.5 (62.7–71.5)	IMT: 6/7 CG: 5/8	IMT: 55 (45–71.2) CG: 75 (67.5–95)	Threshold loading device (Threshold), 1/5 sessions supervised a week	8–10 sets of 5–6 breaths at 40–70% PI_{max}	5 sessions a week for 6 weeks	SHAM-IMT; identical to IMT group but intensity fixed at lowest possible resistance (7 cmH_2O), 6 weeks	PI_{max}, 6MWT, QoL
Aznar-Lain et al. (2007)	2007	9/9	IMT: 68.5 ± 6.3 CG: 67.8 ± 7.5	IMT: 2/7 CG: 2/7	IMT: 54.1 ± 9.2 CG: 67.8 ± 14.4	Threshold loading device (Respironics), supervision not reported.	8–10 sets of 5–6 breaths at 50–80% PI_{max}, 1-minute rest between sets	5 sessions per week (3 during week 1) for 8 weeks	SHAM-IMT; identical to IMT group but intensity fixed at lowest possible resistance (7 cmH_2O), 8 weeks	PI_{max}, $\dot{V}O_2$ peak, Time of Bruce test, time fixed load test. MVPA, total activity counts, total steps, total sitting time and %
Craighead et al. (2021)	2021	18/18	IMT: 67 ± 2 CG: 67 ± 2	IMT: 9/9 CG:10/8	IMT: 64 ± 21 CG: 69 ± 21.2	TFRL (POWERbreathe), 1/6 sessions supervised a week	5 sets of 6 breaths at 55–75% PI_{max}, 1-minute between sets	6 sessions per week for 6 weeks	SHAM-IMT; identical to IMT group but intensity fixed at 15% PI_{max}, 6 weeks	PI_{max}, blood pressure, endothelial function, plasma cytokines
Ferraro et al. (2019)	2019	23/23	IMT: 75 ± 6 CG: 72 ± 5	IMT: 9/14 CG: 9/14	IMT: 76.0 ± 27.4 CG: 72.8 ± 40.9	Threshold loading device (POWERbreathe),	30 breaths, 50% PI_{max}, increased resistance when 30 breaths were	Twice daily, 8 weeks	SHAM-IMT; 60 slow breaths at 15%	Pulmonary function /spirometry, PI_{max}, balance,

						unsupervised, home-based	achievable with ease		PI$_{max}$, once daily, 8 weeks	physical performance
Huang et al. (2011)	2011	24/24	IMT: 70.6 ± 4.8 CG: 70.8 ± 9.1	IMT: 2/22 CG: 2/22	IMT: 59.1 ± 19.2 CG: 58.8 ± 19.1	Threshold loading device, 3/5 sessions supervised a week	4 sets of 6 breaths. Load adjusted to maintain 75% PI$_{max}$ every week	5 sessions per week for 6 weeks	Not reported	PI$_{max}$, 6MWT, QoL, pulmonary function, dyspnoea
Kaneko et al. (2022)	2022	18/17	IMT: 79 ± 6 CG: 76 ± 6	IMT: 13/5 CG: 12/5	IMT: 52.4 ± 20.5 CG: 60.7 ± 19.5	Threshold loading device (Threshold/ POWERbreathe), unsupervised, home-based	5 sets of 5 breaths at 50% PI$_{max}$	At least 5 sessions per week for 4 weeks	No training	PI$_{max}$, PE$_{max}$, pulmonary function, cough peak flow
Mills et al. (2015)	2015	17/17	IMT: 69 ± 3 CG: 68 ± 3	IMT: 9/8 CG: 11/6	IMT: 82 ± 27 CG: 96 ± 27	Threshold loading device (POWERbreathe), unsupervised	30 breaths, 50% PI$_{max}$, increased resistance when 30 breaths were achievable with ease	Twice daily, 8 weeks	SHAM-hypoxic trainer, <5 cmH$_2$O resistance, 30 breaths, twice daily, 8 weeks	Pulmonary function test/spirometry, PI$_{max}$, PE$_{max}$, MVV, Inspiratory muscle endurance, diaphragm thickness, 6MWT, PAL, QoL, plasma cytokines
Rodrigues, Gurgel, Gonçalves, and da Silva Soares (2018)	2018	11/8	IMT: 64 ± 3 CG: 64 ± 4	IMT: 0/11 CG: 0/8	IMT: 84 ± 18 CG: 80 ± 16	Threshold loading device (POWERbreathe, 1/5 sessions supervised a week	30 repetitions, 50% PI$_{max}$. Load adjusted to maintain 50% PI$_{max}$ once a week	5 sessions per week for 5 weeks	SHAM-IMT: identical to IMT group but load at 5% PI$_{max}$	PI$_{max}$, 6MWT, heart rate variability and kinetics

Rodrigues et al. (2020)	2020	8/6	IMT: 63 ± 4 CG: 65 ± 3	IMT: 0/8 CG: 0/6	IMT: 88.2 ± 6.6 CG: 93.3 ± 14.0	Threshold loading device (POWERbreathe, 1/5 sessions supervised a week	30 repetitions, 50% PI_{max}. Load adjusted to maintain 50% PI_{max} once a week	Twice daily, 5 sessions per week for 4 weeks	SHAM-IMT: identical to IMT group but load at 5% PI_{max}	PI_{max}, blood pressure, cerebrovascular, and postural control during rest and orthostatic stress
Rodrigues et al. (2021a)	2021	8/6	IMT: 64 ± 3 CG: 66 ± 3	IMT: 0/8 CG: 0/6	As above	As above	As above	As above	As above	PI_{max}, breathing pattern, heart rate, blood pressure variability, and spontaneous baroreflex reactivity
Rodrigues, Dal Lago, and da Silva Soares (2021b)	2021	6/6	IMT: 63 ± 3 CG: 64 ± 5	IMT: 0/6 CG: 0/6	IMT: 87.7 ± 6.6 CG: 81.7 ± 16.3	As above	As above	As above	As above	Time-dependent effects of IMT and detraining on PI_{max} and heart rate variability
Souza et al. (2014)	2014	12/10	IMT: 68.3 ± 5.2 CG: 68.3 ± 5.3	IMT: 0/12 CG: 0/10	IMT: 73.3 ± 12.2 CG: 79.4 ± 18.4	Threshold loading device (Respironics), supervised once per week	8 cycles of 2-minutes work at 40% PI_{max}, 1-minute rest	Twice daily, 7 weeks	SHAM-IMT: same as IMT group but with no resistance	Diaphragm thickness and mobility, PI_{max}, PE_{max}, pulmonary function test/spirometry
Watsford and Murphy (2008)	2008	13/13	IMT: 64.8 ± 2.5 CG: 64.0 ± 2.9	IMT: 0/13 CG: 0/13	IMT: 69 ± 20 CG: 74 ± 14	Inspiratory and expiratory threshold loading	Hypertrophy sessions: 3 sets of 10 reps at 10RM. Endurance	12 sessions per week, 6 days, 8 weeks.	No training	PI_{max}, PE_{max}, incremental walking test,

			(Powerlung), unsupervised	sessions: 40 breaths at 40RM. Strength sessions: 5 sets of 5 reps at 5RM	Hypertrophy - 8 sessions per week, endurance - 2 sessions, strength - 2 sessions		pulmonary function

6MWT, six-minute walk test; BMI, body mass index; CG, control group; IMT, inspiratory muscle training; PI_{max}, maximal inspiratory pressure; PE_{max}, maximal expiratory pressure; MVPA, moderate to vigorous physical activity; MVV, maximal voluntary ventilation; PAL, physical activity levels; QoL, quality of life; RM, repetition maximum; TFRL, tapered flow resistive loading; $\dot{V}O_2$ peak, peak oxygen uptake.

3.3.1. Characteristics of included subjects

The included studies comprised of 336 participants and had a mean age of 68.2 years (range 64–79) and an average baseline PI_{max} of 73.0 cmH_2O (52–93 cmH_2O). Participants were healthy older adults with no reported diseases that could influence inspiratory muscle strength.

3.3.2. Quality assessment

The risk of bias of included studies is outlined in Table 3-4. Two publications (Rodrigues et al., 2021a; Rodrigues et al., 2020) were combined due to them arising from one large study consisting of similar methods. The mean PEDro score for included studies was 6.8 and ranged from 4 to 9 (fair to excellent), suggesting a fairly low risk of bias towards the main outcome measures.

Table 3-4. PEDro quality scale scores for included studies.

Study name	Eligibility criteria	Random allocation	Concealed allocation	Baseline similarity	Blind subject	Blind therapist	Blind assessor	Measure of >85%	ITT	Group comparison	Point measure	Quality score
Albuquerque et al. (2013)	*			*			*			*	*	5
Aznar-Lain et al. (2007)		*			*		*	*		*	*	6
Craighead et al. (2021)	*	*		*	*		*	*		*	*	8
Ferraro et al. (2019)	*	*		*	*		*			*	*	7
Huang et al. (2011)	*			*				*			*	4
Kaneko et al. (2022)	*	*	*	*			*	*	*	*	*	9
Mills et al. (2015)	*	*		*	*			*		*	*	7
Rodrigues et al. (2018)	*	*		*	*		*			*	*	7
(Rodrigues et al., 2021a; Rodrigues et al., 2020)	*	*		*				*		*	*	6

Rodrigues et al. (2021b)	*	*		*	*		*	*	*	*	8
Souza et al. (2014)	*	*	*	*	*		*	*	*	*	9
Watsford and Murphy (2008)	*	*		*				*	*	*	6

*Yes. Cut-off points for the PEDro scale were excellent (9–11), good (6–8), fair (4–5) and poor (≤3).

3.3.3. Interventions

The majority (n=12) of included studies used a threshold inspiratory loading device for the training, with the addition of one study using a device that delivered both inspiratory and expiratory threshold loading (Watsford & Murphy, 2008). The remaining study (n=1) used TFRL (Craighead et al., 2021). Training protocols used inspiratory pressures that ranged from 30 to 80% PI_{max}, with the majority of studies using training intensities of 30 to 60% PI_{max} (Ferraro et al., 2019; Kaneko et al., 2022; Mills et al., 2015; Rodrigues et al., 2021b; Rodrigues et al., 2020; Rodrigues et al., 2018; Souza et al., 2014). The shortest duration of IMT was 4 weeks (Kaneko et al., 2022; Rodrigues et al., 2021a, 2021b; Rodrigues et al., 2020) and the longest was 8 weeks (Aznar-Lain et al., 2007; Ferraro et al., 2019; Mills et al., 2015; Watsford & Murphy, 2008).

At least one supervised training a week was reported in eight out of the thirteen included studies (Albuquerque et al., 2013; Craighead et al., 2021; Huang et al., 2011; Rodrigues et al., 2021a, 2021b; Rodrigues et al., 2020; Rodrigues et al., 2018; Souza et al., 2014). SHAM-IMT was used in the control condition of ten studies (Albuquerque et al., 2013; Aznar-Lain et al., 2007; Craighead et al., 2021; Ferraro et al., 2019; Mills et al., 2015; Rodrigues et al., 2021a, 2021b; Rodrigues et al., 2020; Rodrigues et al., 2018; Souza et al., 2014), with the control groups within the remaining studies either not participating in any training protocol (Kaneko et al., 2022; Watsford & Murphy, 2008) or was not reported (Huang et al., 2011).

3.3.4. Outcome measures

All studies (n=13) used PI_{max} (cmH_2O) to reflect inspiratory muscle strength as an outcome measure. Three studies used the distance covered during a 6MWT (meters) to reflect functional capacity (Huang et al., 2011; Mills et al., 2015; Rodrigues et al., 2018).

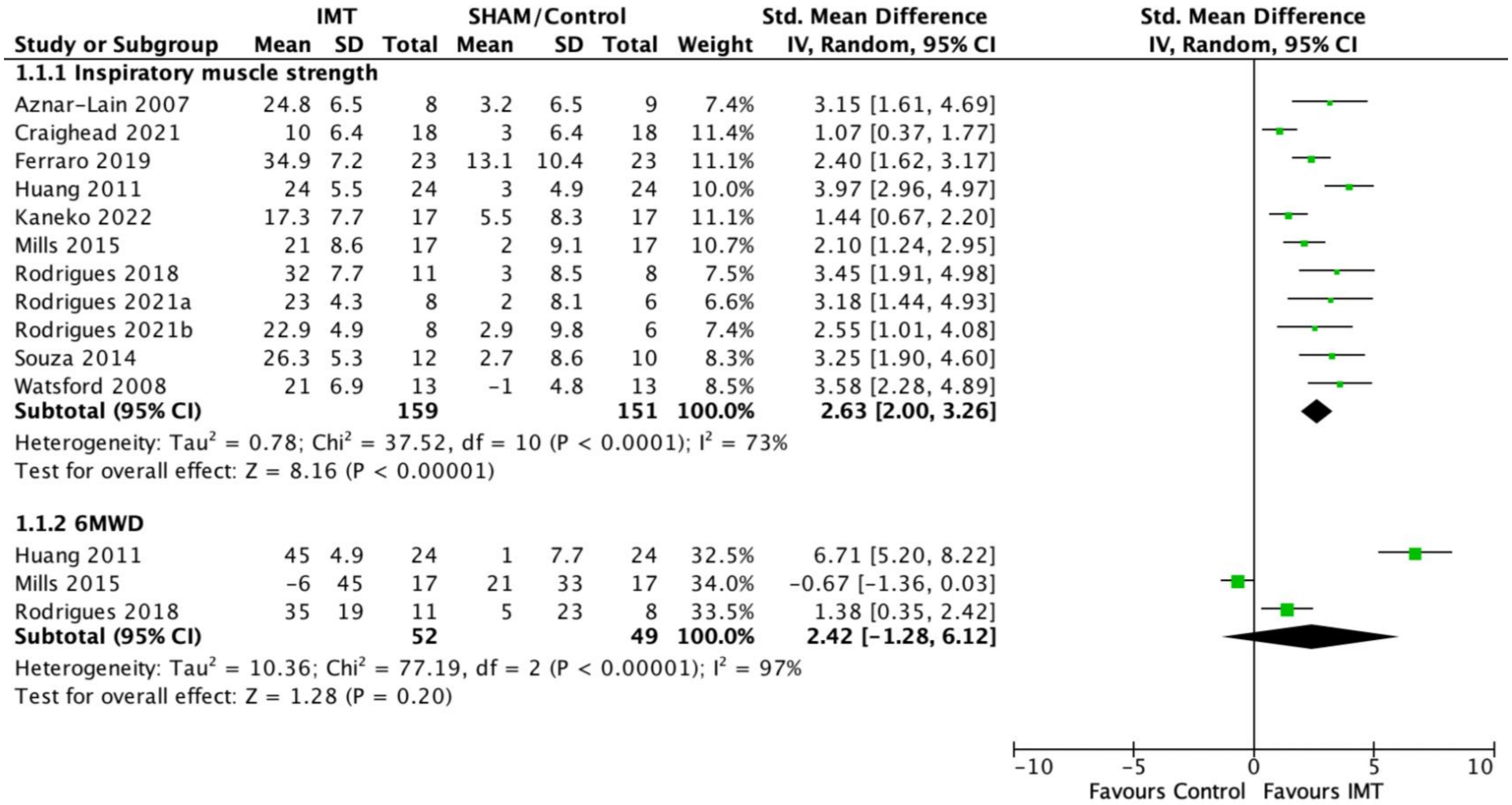
3.3.5. Meta-analyses of included studies

3.3.5.1. Inspiratory muscle strength

Eleven studies (Aznar-Lain et al., 2007; Craighead et al., 2021; Ferraro et al., 2019; Huang et al., 2011; Kaneko et al., 2022; Mills et al., 2015; Rodrigues et al., 2021a, 2021b; Rodrigues et al., 2018; Souza et al., 2014; Watsford & Murphy, 2008) with 310 participants provided mean change scores for pooling. The meta-analysis showed a positive effect of IMT on PI_{max} (n=11, 2.63 [2.00, 3.26], p <0.001; Figure 3-2). The average increase in PI_{max} in the intervention was 23.4±6.7 cmH_2O compared to 3.6±3.5 cmH_2O in the control. The meta-analysis showed substantial heterogeneity (I^2=73%). No significant correlation was found between baseline PI_{max} and post-intervention change in PI_{max} expressed as absolute values (n=11, *r*=0.359, p=0.279; Figure 3-3a) and percentage change from baseline (n=11, *r*=0.301, p=0.368; Figure 3-3b).

3.3.5.2. Six-minute walk distance (6MWD)

Three studies (Huang et al., 2011; Mills et al., 2015; Rodrigues et al., 2018) with 101 participants provided mean change scores for pooling. IMT showed no significant effect on the distance covered during a 6MWT (n=3, 2.42 [−1.28, 6.12], p=0.20; Figure 3-2), however it can be considered to result in a small MCID (Perera et al., 2006). The average increase in 6MWD following IMT was 24.7±22.1 m in the intervention groups compared to 9±8.6 m in the control groups. The meta-analysis showed considerable heterogeneity (I^2=97).



	IMT			SHAM/Control				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
1.1.1 Inspiratory muscle strength								
Aznar-Lain 2007	24.8	6.5	8	3.2	6.5	9	7.4%	3.15 [1.61, 4.69]
Craighead 2021	10	6.4	18	3	6.4	18	11.4%	1.07 [0.37, 1.77]
Ferraro 2019	34.9	7.2	23	13.1	10.4	23	11.1%	2.40 [1.62, 3.17]
Huang 2011	24	5.5	24	3	4.9	24	10.0%	3.97 [2.96, 4.97]
Kaneko 2022	17.3	7.7	17	5.5	8.3	17	11.1%	1.44 [0.67, 2.20]
Mills 2015	21	8.6	17	2	9.1	17	10.7%	2.10 [1.24, 2.95]
Rodrigues 2018	32	7.7	11	3	8.5	8	7.5%	3.45 [1.91, 4.98]
Rodrigues 2021a	23	4.3	8	2	8.1	6	6.6%	3.18 [1.44, 4.93]
Rodrigues 2021b	22.9	4.9	8	2.9	9.8	6	7.4%	2.55 [1.01, 4.08]
Souza 2014	26.3	5.3	12	2.7	8.6	10	8.3%	3.25 [1.90, 4.60]
Watsford 2008	21	6.9	13	-1	4.8	13	8.5%	3.58 [2.28, 4.89]
Subtotal (95% CI)			**159**			**151**	**100.0%**	**2.63 [2.00, 3.26]**
Heterogeneity: Tau^2 = 0.78; Chi^2 = 37.52, df = 10 (P < 0.0001); I^2 = 73%								
Test for overall effect: Z = 8.16 (P < 0.00001)								
1.1.2 6MWD								
Huang 2011	45	4.9	24	1	7.7	24	32.5%	6.71 [5.20, 8.22]
Mills 2015	-6	45	17	21	33	17	34.0%	-0.67 [-1.36, 0.03]
Rodrigues 2018	35	19	11	5	23	8	33.5%	1.38 [0.35, 2.42]
Subtotal (95% CI)			**52**			**49**	**100.0%**	**2.42 [-1.28, 6.12]**
Heterogeneity: Tau^2 = 10.36; Chi^2 = 77.19, df = 2 (P < 0.00001); I^2 = 97%								
Test for overall effect: Z = 1.28 (P = 0.20)								

Figure 3-2. Mean difference (95% CI) from baseline of the effect of inspiratory muscle training on inspiratory muscle strength (measured by maximal inspiratory pressure; n=11) and six-minute walk test distance (n=3) compared to control.

SD, standard deviation, IMT, inspiratory muscle training, 6MWD, six-minute walk distance, CI, confidence interval.

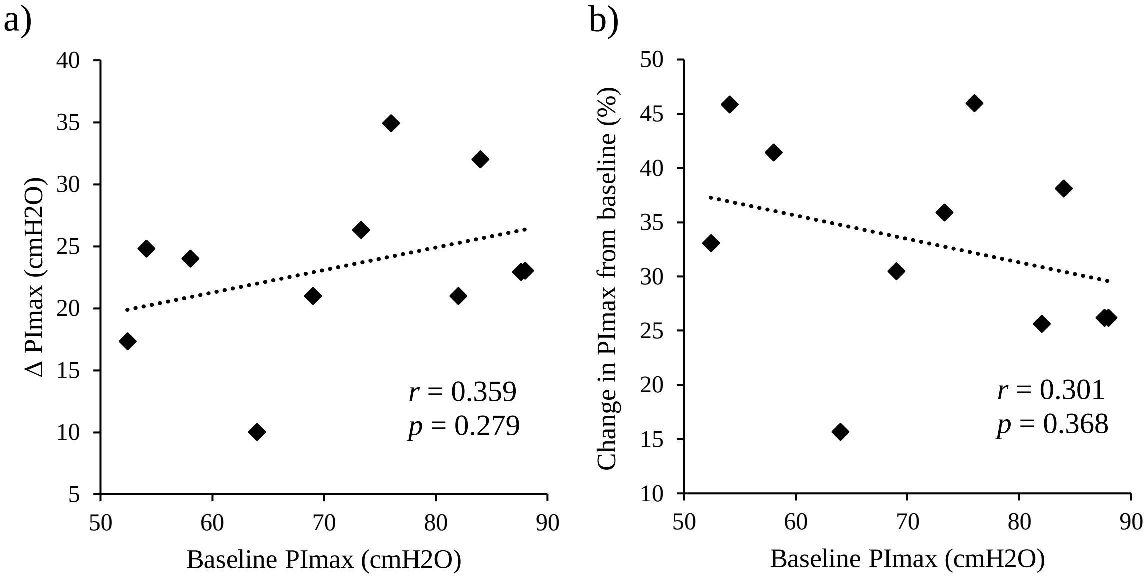


Figure 3-3. The relationship between baseline maximal inspiratory pressure (PI_{max}) values and delta (Δ) PI_{max} (a) and percentage changes in PI_{max} from baseline (b) following training (n=11).

3.4. Discussion

The present systematic review and meta-analysis suggests that specific IMT can significantly increase inspiratory muscle strength, reflected by an increase in PI_{max} (cmH_2O). This meta-analysis showed an effect size of 2.63 (2.00, 3.26) and can be categorised as a huge positive effect (Sawilowsky, 2009). There was no significant change in 6MWD following IMT, however, the improvement observed in this meta-analysis could be considered clinically meaningful as participants improved by over 20 m (Perera et al., 2006). This meta-analysis also showed a large effect size (2.42 [−1.28, 6.12]). Due to the lack of statistical significance, high heterogeneity (I^2=97%), and small number of included studies (n=3), further research is needed to determine the true effect of IMT on functional capacity in healthy older adults.

3.4.1. Interpretation of findings

Previous meta-analyses investigating the effect of IMT have typically reported average increases in PI_{max} in COPD patients by 13 cmH_2O (Gosselink et al., 2011), 11.6 cmH_2O (Geddes et al., 2008) and 16 cmH_2O (Lötters, Van Tol, Kwakkel, & Gosselink, 2002), as well as increase in PI_{max} by 20 cmH_2O (Smart et al., 2013) in CHF patients. The present study suggests that IMT is also beneficial in improving inspiratory muscle strength in older adults without a long-term condition, reflected by an average increase of 23.4±6.7 cmH_2O within the experimental groups compared to a non-significant average change of 3.6±3.5 cmH_2O within the control groups.

The mechanisms of improved PI_{max} following IMT are likely due to structural and functional adaptations to the training stimulus, including increased strength, speed of shortening and power output (Romer & McConnell, 2003). In this case, the majority of studies used a moderate training load of 30–60% PI_{max}, which has been shown to elicit improvements in both maximal shortening velocity and PI_{max} (Romer & McConnell, 2003; Tzelepis et al., 1994) secondary to hypertrophy of inspiratory muscles (Downey et al., 2007; Enright et al., 2006). The present chapter provides evidence that hypertrophy is related to the improvement in PI_{max} as two included studies (Mills et al., 2015; Souza et al., 2014) reported increases in diaphragm thickness following IMT.

The average improvement in functional capacity, reflected by an increase of 24.7±22.1 m, following IMT in older adults within the present meta-analysis did not reach statistical significance. Previous research has used both distribution- and anchor-based methods to determine a small MCID of 20 m and a substantial MCID of 50 m for the 6MWD in community-dwelling older adults (Perera et al., 2006), suggesting that the improvement observed in this meta-analysis may be clinically meaningful. Mills et al. (2015) suggested that the observed lack of improvement in functional capacity was due to participants having a higher predicted baseline 6MWD (102–103%), using predicted values from Troosters, Gosselink, and Decramer (1999), compared to the lower values of 90% in the healthy older group in the study by Huang et al. (2011). Baseline 6MWD values were in line with predicted values for healthy older adults (Troosters et al., 1999). Rodrigues et al. (2018) suggested that the improvement in functional capacity is likely due to a greater improvement in PI_{max} compared to that observed previously (Mills et al., 2015). Furthermore, the greater increase in distance covered (44 m) observed by Huang et al. (2011) could be related to the participants in the IMT group having lower baseline PI_{max} values (59.1 ± 19.2 cmH_2O) compared to Rodrigues et al. (2018; 84 ± 18 cmH_2O) and Mills et al. (2015; 82 ± 27 cmH_2O). It should be noted that the control group used in Huang et al. (2011) consisted of participants with COPD and not older adults without COPD, however baseline values for age, PI_{max}, and 6MWD were similar between groups. Furthermore, 6MWD was also assessed in the study conducted by Albuquerque et al. (2013), with the IMT group showing a significantly increased distance following training (by 25.1 m [−39–40.5 m]) compared to the control group (by −19.6 m [13–79 m]). As this data was reported as median and interquartile range (IQR), it was unable to be included within the present meta-analysis.

Unfortunately, quality of life could not be included as an outcome measure within this meta-analysis due to different questionnaires used between included studies, along with insufficient data reported. Albuquerque et al. (2013) found that IMT had no significant effect on any of the medical outcomes study short form-36 (SF-36) scales, whereas Huang et al. (2011) reported a significant increase in the physical component score following IMT. Mills et al. (2015) used the Older Person’s Quality of Life Questionnaire (OPQOL-35) but did not find any significant changes following the training programme.

IMT has been shown to improve various other outcome measures in older adults, including: increased diaphragm thickness (Mills et al., 2015; Souza et al., 2014), moderate to vigorous physical activity levels (MVPA; Aznar-Lain et al., 2007), time to exhaustion exercise tests (Aznar-Lain et al., 2007), peak oxygen uptake ($\dot{V}O_2$ peak; Aznar-Lain et al., 2007), balance (Ferraro et al., 2019; Rodrigues et al., 2020), maximal expiratory pressure peak inspiratory flow rate (PIFR; Ferraro et al., 2019; Mills et al., 2015), cardiac autonomic modulation

(Rodrigues et al., 2018), decreased blood pressure (Craighead et al., 2021) and dyspnoea scores (Huang et al., 2011). However, some studies report conflicting results including no significant effect of IMT on physical activity levels (Mills et al., 2015), blood pressure (Rodrigues et al., 2021a), and dyspnoea levels (Cebria i Iranzo, Arnall, Igual Camacho, & Tomas, 2014). IMT that induces significant improvements in PI_{max} can also reduce breathlessness in COPD (Hill, Jenkins, Hillman, & Eastwood, 2004) and CHF patients (Laoutaris et al., 2004), however, when Huang et al. (2011) investigated the relationship between the difference in PI_{max} and the difference in dyspnoea scores following IMT in healthy older adults, no significant correlation was observed. The authors suggested that this was due to a ceiling effect as participants reported relatively high baseline dyspnoea scores.

A recent systematic review investigated the effects of IMT in an older population (Seixas et al., 2019). Due to a large heterogeneity in participant characteristics, however, the authors did not perform a meta-analysis on their included studies. Two studies (Cebria i Iranzo et al., 2014; Cebria i Iranzo, Balasch-Bernat, Tortosa-Chuliá, & Balasch-Parisi, 2018) that were included in the review conducted by Seixas et al. (2019) were excluded from the present systematic review and meta-analysis due to a considerable amount of the participants having comorbidities that could significantly affect inspiratory muscle strength. Furthermore, the participants were significantly older than in the remaining studies (84.5 years compared to 68.2 years) and had lower baseline PI_{max} values (33.6 cmH_2O compared to 73.3 cmH_2O). The lack of improvement in PI_{max} following IMT within these two studies (6.7 and 2.8 cmH_2O) contradicts previous literature which has suggested that patients with pronounced inspiratory muscle weakness (PI_{max} <60 cmH_2O) show a better response to IMT in terms of inspiratory muscle strength and functional capacity in COPD (Basso-Vanelli et al., 2016; Gosselink et al., 2011) and CHF (Montemezzo et al., 2014). In the present review, correlation analysis of included studies showed no significant association between baseline inspiratory muscle strength and the post-IMT change in PI_{max} (Figure 3-3a) and percentage change in PI_{max} from baseline (Figure 3-3b), suggesting that IMT is beneficial in older adults regardless of their initial degree of inspiratory muscle weakness. Accordingly, IMT would be beneficial even in older adults with a wide range of inspiratory muscle weakness.

Cebria I Iranzo and colleagues suggested that the lack of improvement following the training programme is likely due to the extreme debilitation and institutionalisation of the older adults (Cebria i Iranzo et al., 2014). Furthermore, a significant improvement in PI_{max} following IMT was only observable when compared to the decreased values within the control group (Cebria i Iranzo et al., 2018). This suggests that IMT in frail older adults with sarcopenia may be beneficial in preventing the age-related decline in respiratory muscle strength, which is evident within this population (Simões, Castello, Auad, Dionísio, & Mazzonetto, 2009).

The study conducted by Albuquerque et al. (2013) was also excluded from the meta-analysis due to the data expressed as median (IQR). Nevertheless, this study showed significant improvements in inspiratory muscle strength and functional capacity following a six-week IMT programme compared to the SHAM-IMT control.

3.4.2. Quality of the evidence

The quality of the included studies ranged from fair to excellent on the PEDro quality scale (Table 3-4). As most of the studies involved mainly unsupervised training sessions, the lack of a blinded therapist in all included studies is unlikely to significantly increase the risk of bias in the present meta-analysis. However, the lack of reported intention to treat and concealed allocation in the majority of included studies reduced the overall quality of the evidence.

3.4.3. Strengths and limitations

This is the first meta-analysis to investigate the effects of IMT during healthy ageing and was conducted in line with both the Cochrane Handbook for Systematic Reviews of Interventions and the PRISMA guidelines. The main limitations of this systematic review and meta-analysis include the considerable heterogeneity along with the lack of reported intention to treat analysis and concealed allocation to groups. The high heterogeneity in the 6MWD meta-analysis is likely due to the variation of methods and participant characteristics between studies, such as the intensity, frequency and duration of IMT along with baseline PI_{max} values. Future research should aim to standardise methods of IMT in this population to reduce heterogeneity, thus, chapter 6 of this thesis will implement the most commonly used IMT protocol identified within this systematic review (30 breaths, twice daily, at 50% PI_{max}). Furthermore, since six studies (Rodrigues et al., 2021a, 2021b; Rodrigues et al., 2020; Rodrigues et al., 2018; Souza et al., 2014; Watsford & Murphy, 2008) were performed in older women only, sex differences could have affected the absolute values for baseline PI_{max}, however, as absolute change scores were used when pooling the data (Figure 3-2), and to show the relationship between baseline and post-intervention changes (Figure 3-3) this is unlikely to have affected the results.

3.4.4. Implications for improving inspiratory muscle strength

By administering IMT to healthy older adults, it may be possible to prevent or delay the decline in inspiratory muscle strength in this population with inexpensive equipment and without requiring significant time. Evidence suggesting that respiratory muscle strength may be at the beginning of a causal chain leading to decreased pulmonary function and mortality (Buchman et al., 2008a) highlights the clinical importance of interventions, such as IMT, that can improve or maintain respiratory muscle strength in healthy older adults.

3.5. Conclusion

Overall, this chapter provides evidence that IMT can be beneficial in an older population without the presence of a long-term condition; however, due to the high heterogeneity and large variation of methods it is difficult to draw concrete conclusions. There is a need for future studies to investigate the effect of IMT on functional capacity and quality of life in healthy older adults, and to determine whether IMT can reduce breathlessness and improve daily physical activity levels, which are associated with mortality in this population (Ahmed, Steward, & O'Mahony, 2012; Manini et al., 2006). Chapter 6 of this thesis will aim to address these aforementioned factors.

CHAPTER 4 - GENERAL METHODS

4.1. Introduction

This chapter details the general methods applied to the studies within this thesis. Specific methods used for individual studies can be found within the respective experimental chapters.

4.2. Pre-test procedures

4.2.1. Ethical approval

Institutional ethical approval was obtained from the Department of Sport, Exercise, and Rehabilitation ethics committee at Northumbria University in accordance with the World Medical Association's Declaration of Helsinki (1975) prior to any data collection for Chapter 5 (ID: 16821), Chapter 6 and 7 (ID: 23701).

4.2.2. Participants

Both young (age: 18–30 years) and older (age: 60–75 years) adults were recruited as participants for the studies within this thesis. Inclusion criteria were followed and included: both healthy adults aged between 18–30 years or 60–75 years (Chapter 5), and only healthy older adults between 60–75 years (Chapters 6 and 7) who were free from injury and able to give full written consent. The exclusion criteria for all experimental chapters were current smokers, chronic pulmonary, cardiac, or neuromuscular disease, and users of medications that affect muscle strength. Initially, each participant read a participant information sheet (Appendices 1 and 2) and eligible participants provided written informed consent (Appendices 3, 4, and 5). The young participants (Chapter 5) were recruited from the student population at Northumbria University whilst the older participants (Chapters 5, 6 and 7) were recruited from the general population via an introductory email outlining the study requirements. Contact details of older participants that had consented to being contacted regarding future studies at the university were obtained via the brain, performance and nutrition group at Northumbria University.

4.3. Baseline measurements

4.3.1. Anthropometry measurements

The date of birth of each participant was recorded prior to experimental testing and converted into age (years). Stature was measured to the nearest millimetre (mm) via a wall-mounted stadiometer (Seca, Bonn, Germany), and body mass was measured to the nearest 0.1 kilogram (kg) using a balance scale (Seca 200, Vogel and Halke, Germany). During these measurements, participants were required to remove any footwear and wear lightweight clothing only.

4.3.2. Pulmonary function measurements

Prior to inspiratory muscle loading (Chapter 5) or exercise testing (Chapter 6), all participants' pulmonary function was assessed via spirometry tests using a metabolic gas exchange analyser (Cortex; Metalyzer 3B, Leipzig, Germany). The cortex device was calibrated in line with the manufacturer's instructions before spirometry manoeuvres were performed. The variables measured included: forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio, and peak expiratory flow (PEF). These tests were performed to determine all participants' eligibility to the study by confirming no presence of pulmonary disease, i.e. FEV_1/FVC: >70%; FEV_1: >80% predicted (Rabe et al., 2007) and were conducted in line with current guidelines (Graham et al., 2019). After a minimum of three manoeuvres were performed, the manoeuvre which showed the highest values were used (Graham et al., 2019). Predicted values were calculated using standardised reference values for spirometry from the Global Lung Function Initiative (GLI) Network (Cooper et al., 2017; Quanjer et al., 2012). Overall, 97,759 records of healthy non-smokers (55.3% females) from 72 centres in 33 countries were shared by the GLI Network and used to derive reference equations for a variety of ethnic groups (Quanjer et al., 2012).

4.3.3. Respiratory muscle function measurements

Maximal inspiratory and expiratory pressures (PI_{max} and PE_{max}) were assessed using a handheld pressure transducer (MicroRPM; Micro Medical Ltd, Rochester, Kent, UK). This device reports the maximum mean inspiratory pressure sustained over a 1 second period of the test in cmH_2O. This measurement technique was chosen for this thesis as it is simple to perform and well tolerated by participants (ATS/ERS statement on respiratory muscle testing, 2002). The disadvantages of this technique are that it is volitional and low values may therefore be due to a lack of motivation and not necessarily reduced respiratory muscle strength (ATS/ERS statement on respiratory muscle testing, 2002).

Other methods of assessing respiratory muscle strength include balloon catheters which can record oesophageal pressure (P_{oes}; as a reflection of pleural pressure [P_{pl}]), gastric pressure (P_{ga}; as a reflection of abdominal pressure [P_{ab}]), and transdiaphragmatic pressure (P_{di}; the difference between P_{pl} and P_{ab}; Laveneziana et al., 2019; ATS/ERS statement on respiratory muscle testing, 2002). Diaphragmatic strength is reflected by P_{di} and can be recorded during a maximal volitional sniff manoeuvre or during stimulation of the phrenic nerve ($P_{di,\ tw}$; ATS/ERS statement on respiratory muscle testing, 2002). Advantages of these measures are that P_{di} is specific for diaphragm contraction, with P_{oes} and P_{ga} providing information on the components of this contraction (ATS/ERS statement on respiratory muscle testing, 2002). Furthermore, phrenic nerve stimulation is nonvolitional and therefore eliminates variation due to participant motivation (Polkey, Green, & Moxham, 1995). The disadvantages of using these techniques are that the participants may face some discomfort when swallowing the balloon catheters and during evoked stimulation of the diaphragm. Furthermore, these techniques require specialist equipment and trained staff which were unavailable to us at the time.

Participants in this thesis were seated and performed forceful inspiratory efforts (Mueller manoeuvre) from both RV and FRC for PI_{max}, and forceful expiratory efforts (Valsalva manoeuvre) from TLC for PE_{max}, for at least 1.5 seconds against an occluded airway (Laveneziana et al., 2019). Initially, participants performed 3 inspiratory muscle warm up manoeuvres at self-determined 50% and 3 at 75% PI_{max} in order to be familiarised with the manoeuvre. Maximal measurements were repeated at least five times until three consecutive manoeuvres had less than 10% variability with the highest of these values used (Laveneziana et al., 2019).

Previous research has aimed to determine the level of agreement among frequently used PI_{max} prediction equations to suggest weakness (Rodrigues et al., 2017). The authors found that prevalence of weakness varied widely depending on the chosen set of reference values, and that set 2 equations (Black & Hyatt, 1969; Bruschi et al., 1992; Neder, Andreoni, Lerario, & Nery, 1999) had superior agreement to suggest weakness than set 1 equations (Enright et al., 1994; Harik-Khan, Wise, & Fozard, 1998; Wilson, Cooke, Edwards, & Spiro, 1984). Predicted PI_{max} values (cmH_2O) were, therefore, calculated using equations outlined by Black and Hyatt (1969) for males:

$$143 - (0.55 \times age)$$

and females:

$$104 - (0.51 \times age)$$

The above equations were used to determine the percentage predicted (%pred) PI_{max} values for each participant.

4.4. Testing instrumentation and procedures

4.4.1. Operational thoracoabdominal volume measurements

Operational thoracoabdominal volumes were measured by OEP (BTS Bioengineering, Milan, Italy) during QB (Chapter 5 and 6), inspiratory muscle loading (Chapter 5), and CWR exercise (Chapter 6).

Measurements of pulmonary ventilation via a spirometer or pneumotachograph can be affected by temperature, humidity and pressure, and mouthpieces, face masks, and nose-clips can introduce leaks and additional dead space, whilst interfering with natural breathing patterns by making the participant aware that their breathing is being measured (Aliverti & Pedotti, 2014; Gilbert, Auchincloss Jr, Brodsky, & Boden, 1972). Technological developments in 3D motion capture systems have led to the use of indirect assessments of chest wall surface movement, such as OEP, capable of measuring breath-by-breath changes of the thoracoabdomen (Parreira et al., 2012). This system allows for the non-invasive measurements of total and compartmental V_T, end-inspiratory (V_{EI}) and end-expiratory (V_{EE}) volumes, along with total respiratory cycle time (Ttot), inspiratory time (Ti), expiratory time (Te), breathing frequency, and $\dot{V}_E$. These variables were measured in the experimental chapters of this thesis (Chapters 5 and 6). V_{EE} was set to zero at QB and V_{EI} was defined as $V_{EE} + V_T$. Both V_{EE} and V_{EI} were expressed as changes from baseline within this thesis, and as both absolute values (L) and as percentages of FVC (%FVC) in order to normalise for lung size.

In order to capture this, eight infrared cameras (Smart System, BTS Bioengineering, Milan, Italy), positioned around the participants, tracked infrared-reflective markers (which were attached to their chest wall) in a previously calibrated space (Massaroni et al., 2017). The participants were seated in an upright position, and grasped handles located laterally and positioned in line with their mid sternum to ensure that their arms were lifted away from their chest wall (Figure 4-1). During QB measurements at baseline and following 3–4 normal tidal breaths, the participants were instructed to perform a maximal IC manoeuvre from FRC to TLC as previously described (O'Donnell & Webb, 1993). This manoeuvre was repeated at least twice to ensure accurate measurements.


[redacted]

Figure 4-1. The participant set-up for optoelectronic plethysmography (OEP) measurements during inspiratory muscle loading (chapter 5) and constant work rate exercise (chapter 6). Note: PhysioFlow electrodes also attached to participant (outlined in chapter 6).

Initially, a static calibration was performed to correct optical distortions (Ferrigno, Borghese, & Pedotti, 1990; Parreira et al., 2012) by assembling a three-dimensional (3D) x-y-z axis and positioning it where the participant will be sat, ensuring the visibility of the axis in all cameras. Once this axis was recorded for five seconds, the axis was disassembled into a wand (Y axis), and a dynamic calibration was performed to determine geometric parameters of the collinearity equations used to calculate 3D coordinates based on the real coordinates of a set of control points with a known location (Ferrigno et al., 1990; Parreira et al., 2012). This dynamic calibration lasted two minutes and involved the researcher moving the wand horizontally and vertically above the seat, covering the space in which the participant will later occupy. A ‘convergence’ icon showing three or less bars following this recording determined the successfulness of the calibration.

An 89-marker protocol (Bioengineering, 2011) was followed when using OEP for the assessment of operational thoracoabdominal volumes within this thesis. This involved attaching 89 6- and 10- mm diameter hemispherical or spherical markers (Massaroni et al., 2017) arranged on different levels in anatomical structures between the sternal notch and the clavicles to the anterior superior iliac crest (Aliverti & Pedotti, 2002; Parreira et al., 2012). An example of the OEP marker set-up on a participant tested within this thesis is shown in Figure 4-2. Overall, 37 markers were attached to the anterior, 42 to the posterior, and 10 laterally on each participant (Aliverti & Pedotti, 2002). The OEP workstation synchronises the input and output information to and from each camera and computes 3D trajectories of the markers, before applying a geometrical model via stereophotogrammetry (Massaroni et al., 2017). Within this geometrical model, a closed surface is defined by connecting each triplet of markers to form a triangle, with the volume contained in each triplet calculated from each closed surface (Massaroni et al., 2017). Gauss’s theorem is used to determine the volume within each triangle, shown by the following equation:

$$\int_{S_{cw}} \vec{F} \cdot \vec{n} \, \mathrm{d}S_{cw} = \int_{V_{cw}} \mathrm{d}V_{cw} = V_{cw}$$

where S_{CW} is the closed chest wall surface, V is the volume enclosed by S_{CW}, F is an arbitrary vector, and n is the outward-pointing unit normal vector at the different points of S_{CW} (Aliverti & Pedotti, 2014).

When passing from continuous to discrete form, the equation above becomes:

$$\sum_{i=1}^{K} \vec{F} \cdot \vec{n}_i A_i = V_{cw}$$

Where K is the total number of triangles, A_i is the area of the *i*th triangle, and n is the normal unit vector of the *i*th triangle. This equation allows the direct computation of the volume enclosed by the entire thoracoabdominal surface approximated by a closed mesh of triangles (Aliverti & Pedotti, 2014).

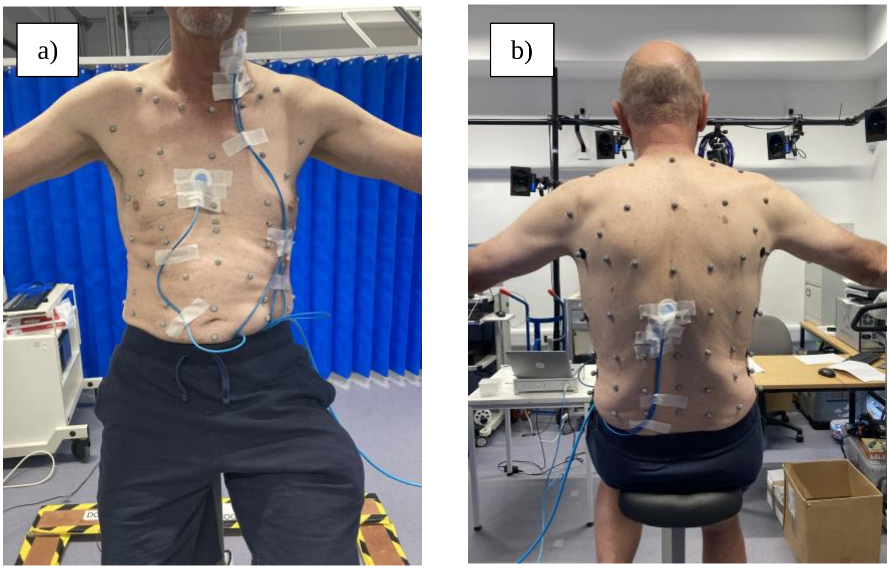


Figure 4-2. The optoelectronic plethysmography (OEP) marker set-up for the front (*a*) and back (*b*) of the participant during inspiratory muscle loading (chapter 5) and constant work rate exercise (chapter 6). Four cameras positioned around the front of the participant are visible in the right panel (*b*). Note: PhysioFlow electrodes also attached to participant (outlined in chapter 6).

The positioning of the markers on the thoracoabdominal surface is designed to allow adequate sampling of its complex shape and subdivision of the total volume into three different compartments: the pulmonary rib cage (RCp), the abdominal rib cage (RCa), and the abdomen (AB; Figure 4-3; Aliverti & Pedotti, 2002, 2014). This allows for the detailed study of respiratory muscle kinematics as it takes into consideration the different pressures that the lung- (RCp) and diaphragm-apposed (RCa) sections of the rib cage are exposed to during inspiration (Agostoni & d'Angelo, 1985; Aliverti & Pedotti, 2002). Furthermore, it also allows for the consideration that the diaphragm acts directly on RCa, and non-diaphragmatic inspiratory muscles (such as the external intercostals, parasternal, scalene, and neck muscles) act largely on RCp only (Aliverti & Pedotti, 2002; Massaroni et al., 2017). These two compartments of the rib cage can be combined to form a total rib cage (RC) compartment. The change in abdominal volume is defined as the volume swept by the abdominal wall (Konno & Mead, 1967), resulting from the action of the diaphragm during inspiration and muscles of the abdominal wall (such as the rectus and transverse abdominis, and the internal and external obliques) during expiration (Aliverti & Pedotti, 2014).

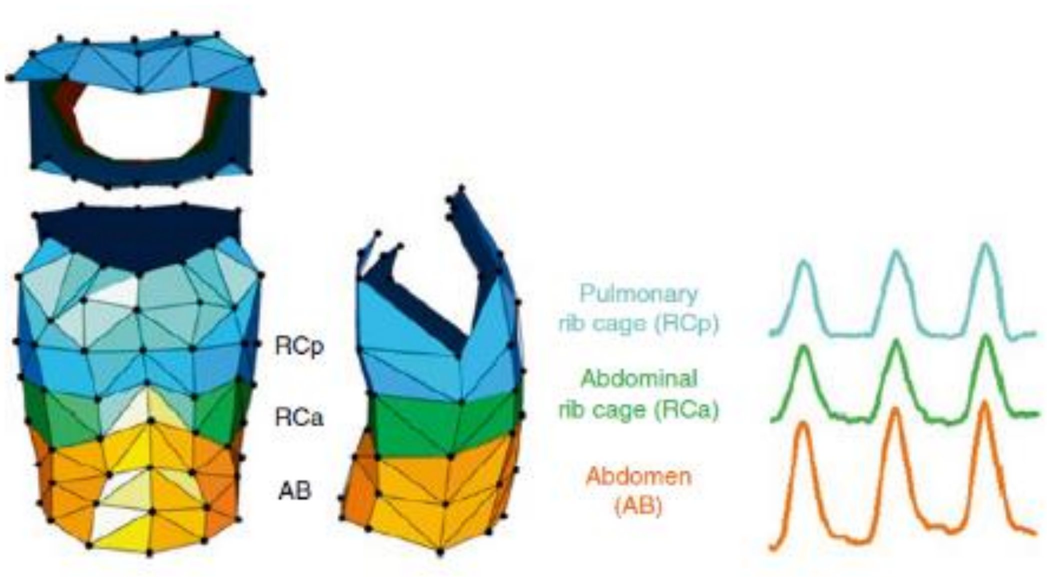


Figure 4-3. The geometrical models of the three thoracoabdominal compartments: the pulmonary rib cage (RCp), the abdominal rib cage (RCa), and the abdomen (AB; left), and their respective volume changes during quiet breathing (V_{RCp}, V_{RCa}, and V_{AB}; right). *Note:* total thoracoabdominal volume (total V) is equal to $V_{RCp} + V_{RCa} + V_{AB}$ (Aliverti & Pedotti, 2014).

The validity of OEP has been assessed by comparing chest wall volume variation, measured by OEP, and lung volume variation, measured by a spirometer (Aliverti et al., 2001; Cala et al., 1996; Kenyon et al., 1997). These studies involved testing healthy participants whilst standing or sitting during QB, slow vital capacity manoeuvres (Cala et al., 1996), during incremental cycle ergometer exercise (Kenyon et al., 1997), and in supine and prone positions (Aliverti et al., 2001). A coefficient of variation between OEP and spirometry values was found to be less than 4% during standing, sitting, and incremental exercise, and less than 5% in supine and prone positions.

OEP has been shown to have a 30μm threshold for detecting linear movement (Bastianini, Schena, & Silvestri, 2012), corresponding volume threshold of 9 ml change in thoracoabdominal volume in typical adults (Massaroni et al., 2017). Simultaneous measurements of V_T by OEP and pneumotachography provided evidence that OEP is accurate in measuring V_T in healthy adults during submaximal (−2.0 ± 7.2%) and maximal (2.4 ± 3.9%) cycling exercise (Layton et al., 2013). Furthermore, intra- and inter-rater reliability assessment of OEP during rest and submaximal cycle-ergometer exercise has found an ICC values >0.75 and a coefficient of variation of method error values <10% for most variables in both conditions, indicating that OEP is a reliable tool for measuring thoracoabdominal volumes (Vieira, Hoffman, Pereira, Britto, & Parreira, 2013).

4.4.2. Perceived symptoms measurements

Participants rated their breathing discomfort following TFRL (Chapter 5), as well as dyspnoea and leg discomfort during exercise (Chapter 6) using the modified Borg scale (Borg, 1982). Furthermore, perceived breathing discomfort was assessed using the same scale following 30 breaths of IMT at 50% of baseline PI_{max} within chapter 6. Post-intervention assessments were recorded after 30 breaths of IMT at the same absolute intensity as pre-intervention.

The modified Borg scale was developed as a categorical scale with ratio properties whereby the numbers are anchored by simple, understandable verbal expressions (Borg, 1982). The points on this scale reflect specific levels of discomfort, ranging from 0 (nothing at all) to 10 (maximal). The different verbal expressions were placed where they belong on the scale according to their ratio properties (Borg, 1982). Participants were instructed prior to testing procedures that “0” on the Borg scale meant no discomfort at all and “10” indicated the worst sensation of breathlessness imaginable. The Borg scale has been shown to be more reproducible than a visual analogue scale for the measurement of dyspnoea during exercise in healthy individuals (Wilson & Jones, 1989).

As dyspnoea is a multidimensional symptom, a more detailed assessment of dyspnoea quality may have been appropriate, however this was not included within this thesis. In brief, this may have included using descriptor phrases for evaluation during exercise, such as: 1) “my breathing requires more work/effort” (work and effort); 2) “I cannot get enough air in” (unsatisfied inspiration/air hunger); 3) “I cannot get enough air out” (unsatisfied expiration); 4) “my chest is constricted/feels tight” (chest tightness) or 5) none apply (Laveneziana, Webb, Ora, Wadell, & O'Donnell, 2011; Laviolette & Laveneziana, 2014; Zhang et al., 2020).

CHAPTER 5 – ACUTE THORACOABDOMINAL VOLUME REGULATION DURING TAPERED FLOW RESISTIVE LOADING IN YOUNGER AND OLDER ADULTS

5.1. Introduction

As outlined in chapter 2, IMT aims to functionally overload the inspiratory muscles and has been shown to improve inspiratory muscle strength (reflected by increased PI_{max}), endurance and exercise tolerance in healthy individuals (McConnell & Romer, 2004), as well as in various respiratory (Enright et al., 2004; Gosselink et al., 2011) and cardiovascular disorders (Dall'Ago et al., 2006). It was determined in chapter 3 that healthy older adults can also benefit from this training.

The acute physiological effects of inspiratory muscle loading has been previously assessed in younger (da Fonsêca et al., 2019; McConnell & Griffiths, 2010; Ross et al., 2007) and older adults (de Souza et al., 2016; Rodrigues, Gurgel, Gonçalves, & da Silva Soares, 2021). de Souza et al. (2016) utilised OEP techniques to investigate the age-related differences in thoracoabdominal volume regulation during QB and during moderate inspiratory resistance via pressure-threshold loading in healthy young and older women. The authors observed greater abdominal volume contribution (Vab%) to V_T in older adults during quiet QB compared to younger individuals. Furthermore, during moderate inspiratory resistance (40% PI_{max}), Vab% was similar to pulmonary rib cage volume contribution (Vrcp%) in older adults whilst Vrcp% was predominant in younger adults (de Souza et al., 2016). The authors suggested that Vab% prevails in older adults as an adaptive response to the decreased compliance of the chest wall during healthy ageing.

A more recently developed TFRL device provides a tapered resistance via an electronic, dynamically adjusted valve allowing pressure to be volume-dependently tapered once the initial threshold has been overcome (Langer et al., 2015). Use of this device in an IMT programme in patients with COPD has resulted in greater improvements in inspiratory muscle function (i.e. strength, endurance, power, and shortening velocity) as well as a greater tolerance of higher training loads compared to those patients who trained with the pressure-threshold loading devices (Langer et al., 2015).

Recent studies have begun to investigate total and compartmental thoracoabdominal volume regulation via OEP during TFRL in healthy younger (da Fonsêca et al., 2019) and in mouth-breathing children (da Fonsêca et al., 2022; da Fonsêca et al., 2020). This research group has observed significant increases in V_{EI} RCp and RCa volumes and observed increased EMG activity in the sternocleidomastoid, scalene and intercostal muscles during inspiratory muscle loading at both 20 and 40% PI_{max} in healthy adults compared to QB (da Fonsêca et al., 2019), highlighting the importance of the rib cage muscles in increasing V_T expansion during TFRL. At present, it is unclear whether, due to the aforementioned physiological changes in the respiratory system during the healthy ageing process, there are age-related differences in thoracoabdominal volume regulation during various intensities of TFRL.

The aims of this chapter were threefold: 1) to investigate thoracoabdominal volume regulation, gas exchange responses and ratings of breathlessness between TFRL at low, moderate, and high intensities; 2) to investigate the effects of age on these variables across different intensities of TFRL; and 3) to investigate whether maximising V_T and reducing breathing frequency reduces sensations of breathlessness and hypocapnia during different intensities of TFRL. It was hypothesised that, due to the aforementioned age-related changes within the respiratory system, older adults would show less V_T expansion of the RC compartments during TFRL compared to their younger counterparts. Furthermore, it was hypothesised that performing TFRL at a reduced breathing frequency (6 breaths/min) with maximised V_T would result in significantly lower levels of hypocapnia and breathlessness in both age groups compared to TFRL at 10 breaths/min.

5.2. Methods

5.2.1. Study design

This was a cross sectional study approved by Northumbria University Newcastle Ethics Committee (No: 16821). The study investigated the acute effects of TFRL at 30, 50 and 70% PI_{max} on thoracoabdominal volume regulation, partial pressures of end-tidal gas responses, and perceived breathlessness in healthy young and older adults. All trials were conducted in one visit.

5.2.2. Participants

Thirteen healthy younger adults and twelve healthy older adults were recruited to take part in the study following inclusion and exclusion criteria outlined in chapter 4. All participants provided full informed consent prior to their participation (Appendix 3).

5.2.3. Participant preparation

Upon arrival to the laboratory, participants performed pulmonary function tests and PI_{max} measurements as outlined in chapter 4. Participants were then familiarised with the TFRL device (POWERbreathe KH1; HaB International Ltd., Southam, UK; Figure 5-1).

Figure 5-1. The POWERbreathe KH1 device which was used to apply acute tapered flow resistive loading to the inspiratory muscles.

5.2.4. Application of acute inspiratory muscle loading

The POWERbreathe KH1 device was used in the present study to apply TFRL to the inspiratory muscles. As outlined in chapter 2, TFRL devices provide a tapered resistance via an electronic, dynamically adjusted valve which allows pressure to be volume-dependently tapered once the initial threshold resistance has been overcome by the participants (Langer et al., 2015).

Participants performed 4 separate trials within the present study. The first and third minute involved QB with the load (30, 50, or 70% PI_{max}) being applied during the second minute via the TFRL device. During the second minute participants breathed at a fixed breathing frequency of 10 breaths per minute (2 s inspiration, 4 s expiration) as outlined by McConnell (2013). An unloaded trial was performed prior to the loaded trials which involved participants breathing at the fixed breathing frequency but without using the device during the second minute. Breathing frequency was controlled to standardise inspiratory muscle loading and to allow the direct comparison of thoracoabdominal volumes between loaded trials at different resistive loads. This frequency was controlled by an interval timer which provided auditory cues signalling when participants should initiate inspirations and expirations. The participants were instructed to inhale forcefully against the resistance during the loaded minute but were given no instructions to expire to RV. This allowed for differences in V_{EE} and fractional contribution of the RC and AB thoracoabdominal compartments to total V_T expansion between inspiratory muscle loaded intensities to be observed. During expiration, there was no resistance, and the load was applied in a balanced ordered sequence for both males and females. For all variables, the QB values reported were averages of the first unloaded minutes within all trials.

A sub-group of 7 younger and 9 older participants repeated each inspiratory loaded trial with a different breathing pattern. As previously, the first and third minute involved QB with no instructions relating to breathing pattern. During the loaded minute, participants were instructed to perform full vital capacity breaths at a fixed frequency of 6 breaths per minute (3 seconds inspiration, 7 seconds expiration), with each loaded inspirations being initiated at RV and expirations initiated at TLC as previously recommended (Langer et al., 2015; Van Hollebeke, Gosselink, & Langer, 2020). This allowed for thoracoabdominal volume regulation, Borg ratings, and end-tidal gas responses to be compared between protocols with different breathing patterns at the same relative intensities.

During all trials, total and compartmental thoracoabdominal V_T, percentage contribution, V_{EI} and V_{EE}, along with $\dot{V}_E$, breathing frequency, inspiratory and expiratory flows were measured continuously via OEP (outlined in chapter 4). Partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) and partial pressure of end-tidal oxygen ($P_{ET}O_2$) were measured on a breath-by-breath basis throughout QB and all TFRL trials by a metabolic gas exchange analyser (Cortex; Metalyzer 3B, Leipzig, Germany). This was achieved by attaching the pick-up lead of the gas exchange analyser to the mouthpiece of the TFRL device. Perceived ratings of respiratory effort were reported by participants following each trial as described in chapter 4.

5.2.5. Statistical analysis

Normal distribution was assessed using the Shapiro-Wilk test, with a p value >0.05 indicating normally distributed data. Where normally distributed, data are presented as mean ± standard deviation (SD). Baseline characteristics between groups were assessed via independent t-tests, and two-way repeated measures ANOVAs with Bonferroni adjustments were used to determine within group (trial [QB, unloaded, 30, 50, and 70% PI_{max}] and TFRL protocol [10 breaths vs. 6 breaths]) and between group (age group [young vs. older]) interactions. Pearson's correlation analysis was performed in order to determine the association between RC volume and total thoracoabdominal volume, as well as between AB volume and total thoracoabdominal volume during inspiratory loaded trials. T-tests were employed to determine differences in regression slopes both between and within age groups.

Where not normally distributed, data are presented as median (IQR), and Friedman tests were used to determine changes across trials for all variables before Wilcoxon tests were applied to determine between trial differences within age groups. The Mann-Whitney *U* test was used to assess differences between age groups. The software IBM SPSS Statistics 26 was used to conduct the analysis and the level of significance for all analyses was set at $p < 0.05$.

5.3. Results

5.3.1. Participant baseline characteristics

Demographic, spirometric, and respiratory muscle strength variables for younger and older participants are outlined in Table 5-1. Younger individuals showed significantly higher values for absolute FEV_1 (p=0.023), FEV_1/FVC (p=0.032), absolute PEF (p=0.028), and absolute PI_{max} (p=0.027). When expressed as percentage predicted values, older adults had significantly higher FEV_1 (p=0.046).

Table 5-1. Participant baseline characteristics.

	Younger adults (n=13)	**Older adults (n=12)**	***p* value**
Age (years)	25 ± 3	67 ± 3	<0.001*
Sex (male/female)	7/6	6/6	N/A
Stature (cm)	173.2 ± 7.4	170.0 ± 9.4	0.374
Mass (kg)	73.6 ± 12.0	74.3 ± 12.1	0.896
FEV_1 (L)	3.8 ± 0.7	3.0 ± 0.8	0.023*
FEV_1 (% predicted)	97.0 ± 13.5	108.1 ± 11.2	0.046*
FVC (L)	4.7 ± 0.8	4.0 ± 1.0	0.087
FVC (% predicted)	100.5 ± 11.8	109.0 ± 10.0	0.074
FEV_1/FVC (%)	81.7 ± 6.4	76.5 ± 4.4	0.032*
PEF (L/s)	8.6 ± 1.7	6.8 ± 1.9	0.028*
PEF (% predicted)	102 ± 12	97 ± 16	0.448
PI_{max} (cmH_2O)	102.1 ± 20.1	78.5 ± 27.5	0.027*
PI_{max} (% predicted)	96 ± 22	90 ± 25	0.554
IC (L)	2.95 ± 0.49	2.65 ± 0.87	0.297

Data presented as mean±SD. FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow; PI_{max}, maximal inspiratory pressure.

5.3.2. Operational thoracoabdominal volume changes during inspiratory muscle loading

As the majority of data collected via OEP were not normally distributed, non-parametric statistical tests were performed. Significant changes in total end-inspiratory thoracoabdominal volumes (total V_{EI}) were observed across all intensities in both younger (p <0.001) and older (p <0.001) age groups. Subsequent Wilcoxon tests showed that, within the younger group, these changes were due to significant increases in total V_{EI} from both QB and unloaded values at all loaded intensities (30, 50, and 70% PI_{max}; Figure 5-2). The older group showed a similar response, however, the increase in total V_{EI} at 70% PI_{max} failed to reach statistical significance when compared to the unloaded value. No significant differences in total V_{EI} were observed between loaded intensities in the younger adults, with a significant decrease at 70% compared with 30% PI_{max} observed within the older group. A similar response was observed when values were normalised for lung size and expressed as %FVC (Figure 5-3).

Increased total V_{EI} during TFRL within the younger groups was induced by significant changes in V_{EI} within all thoracoabdominal compartments (i.e. $V_{RCp,\ EI}$, p=0.001); $V_{RCa,\ EI}$,

$p<0.001$); and $V_{AB, EI}$ $p=0.001$). Wilcoxon tests specifically showed significant increases at each loaded intensity when compared to QB values. Furthermore, V_{EI} within each compartment was significantly increased from unloaded values, except $V_{AB, EI}$ at 70% PI_{max} ($p=0.055$). No differences in compartmental V_{EI} were observed between loaded intensities in the younger adults.

In regards to the older group, significant changes in V_{EI} were also observed for all thoracoabdominal compartments ($V_{RCp, EI}$, $p<0.001$; $V_{RCa, EI}$, $p<0.001$; and $V_{AB, EI}$ ($p=0.014$). These changes were attributed to increases from QB values in $V_{RCp, EI}$ and $V_{RCa, EI}$ at 30 ($p=0.002$ for both), 50 ($p=0.005$ and $p=0.002$), and 70% ($p=0.004$ for both) PI_{max}, along with $V_{AB, EI}$ at 30% PI_{max} only ($p=0.008$). Furthermore, when compared to unloaded values, V_{EI} was significantly increased within the RCp at 30 ($p=0.004$) and 50% ($p=0.041$) PI_{max}; 30 ($p=0.003$), 50 ($p=0.003$), and 70% ($p=0.008$) PI_{max} within the RCa, but did not differ at any loaded intensity within the AB compartment. Significant differences were, however, observed between loaded intensities for $V_{AB, EI}$ only, specifically between 30 and 50% PI_{max} ($p=0.041$), and 30 and 70% PI_{max} ($p=0.028$).

V_{EI} were mostly similar between age groups at each level, however, total V_{EI} was significantly higher in the younger group, compared to their older counterparts, at 70% PI_{max} when expressed as absolute values only ($p=0.030$), which was attributable to a higher absolute $V_{RCp, EI}$ at this intensity ($p=0.034$). When expressed as %FVC, total V_{EI} was significantly higher in the older adults compared to younger adults at QB ($p=0.019$), which was attributable to a greater $V_{AB, EI}$ during QB ($p=0.002$; Figure 5-3). Furthermore, during 30% PI_{max}, older adults had a greater $V_{AB, EI}$ compared to their younger counterparts ($p=0.038$).

Within the younger group, TFRL induced significant changes in total V_{EE} ($p<0.001$), and its compartments ($V_{RCp, EE}$: $p=0.036$; $V_{RCa, EE}$: $p=0.039$; and $V_{AB, EE}$: $p<0.001$; Figure 5-2). For total V_{EE}, significant decreases were observed at all intensities when compared to QB (unloaded: $p=0.008$; 30%: $p=0.019$; 50%:, $p=0.004$; and 70%: $p=0.001$) along with at 50 ($p=0.015$) and 70% ($p=0.005$) PI_{max} when compared to unloaded breathing at the same breathing frequency. A significant decrease in total V_{EE} at 70% compared to 30% (p=0.012) was also observed in younger individuals. Within the RCp compartment, $V_{RCp,\ EE}$ was significantly reduced compared to QB values at 50 (p=0.028) and 70% (p=0.007) PI_{max}, as well as at 70% when compared with unloaded (p=0.041) and 50% (p=0.028). Significant increases were observed from QB values for $V_{RCa,\ EE}$ at 50 (p=0.019) and 70% (p=0.004) PI_{max}, as well as from unloaded values at 70% PI_{max} only (p=0.050).

For older adults, TFRL induced significant changes in total V_{EE} (p=0.0027), attributable to significant changes in $V_{AB,\ EE}$ only (p=0.002). Changes in total V_{EE} were due to decreases compared to QB values during unloaded (p=0.0041), 50 (p=0.019), and 70% (p=0.003) PI_{max}, along with at 70% PI_{max} only when compared to unloaded values (p=0.041). Within the AB compartment, older adults significant reduced $V_{AB,\ EE}$ when compared to QB at 30 (p=0.041), 50 (p=0.008), and 70% (p=0.003) PI_{max}, as well as at 50 (p=0.026) and 70% (p=0.008) PI_{max} when compared to unloaded values. Furthermore, a significant reduction in $V_{AB,\ EE}$ was observed at 50 compared to 30% PI_{max} (p=0.012).

V_{EE} at each intensity were mostly similar between young and older adults, however, $V_{RCa,\ EE}$ was significantly higher in older adults during 70% PI_{max} compared to their younger counterparts when expressed as both absolute values (p=0.008) and %FVC (p=0.026).

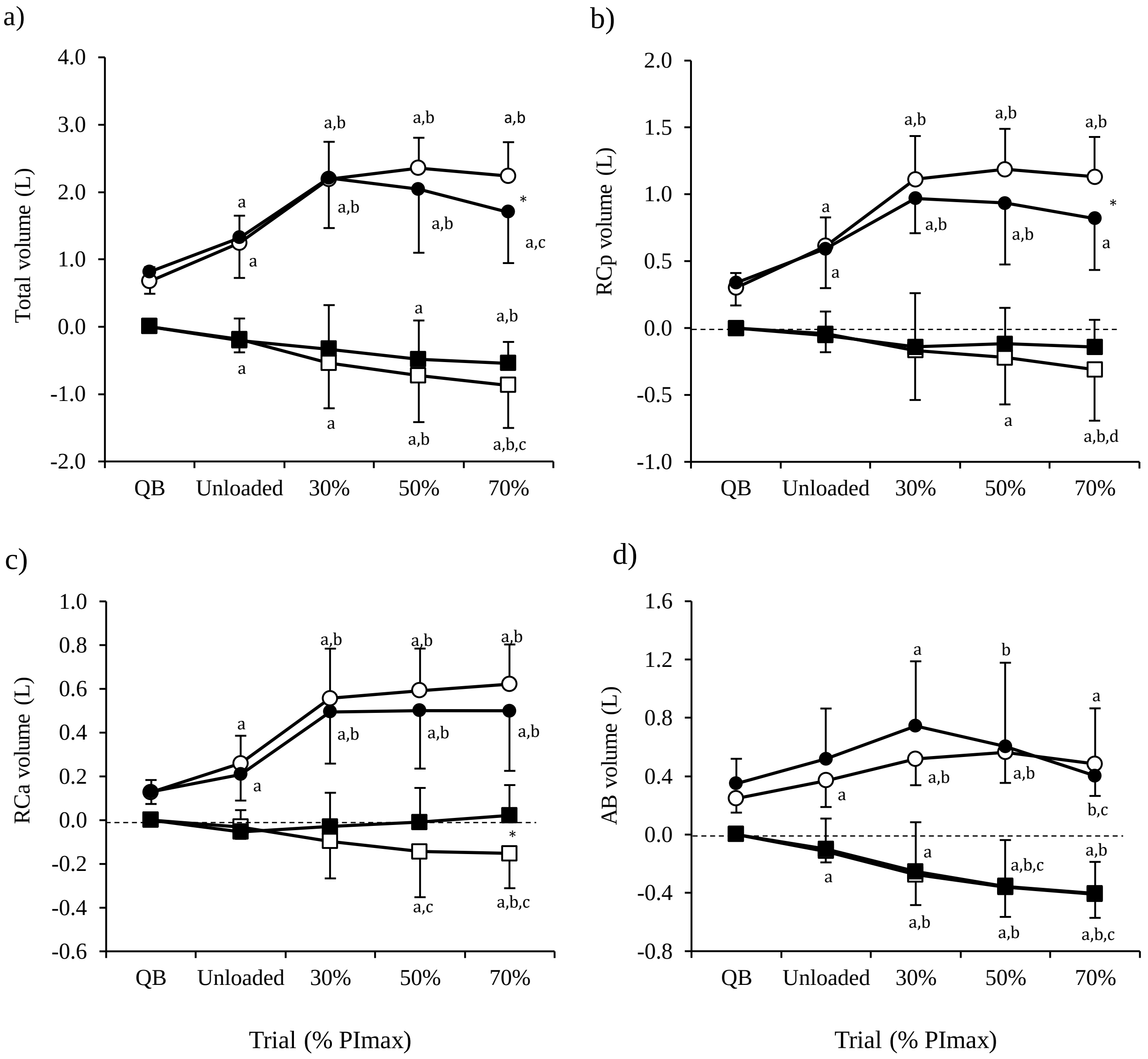


Figure 5-2. Volume changes of the a) total thoracoabdomen, b) the pulmonary rib cage (RCp), c) the abdominal rib cage (RCa) and d) the abdomen (AB) in younger (*open symbols*) and older (*closed symbols*) adults during TFRL at 10 breaths/min expressed as absolute values (L). *Circles* indicate end-inspiration and *squares* indicate end-expiration. *Dashed line* indicates end-expiratory volume (V_{EE}) at quiet breathing (QB). ^{a} significant difference from QB, ^{b} significant difference from unloaded, ^{c} significant difference from 30%, ^{d} significant difference from 50%, * significant difference between age groups at corresponding intensity.

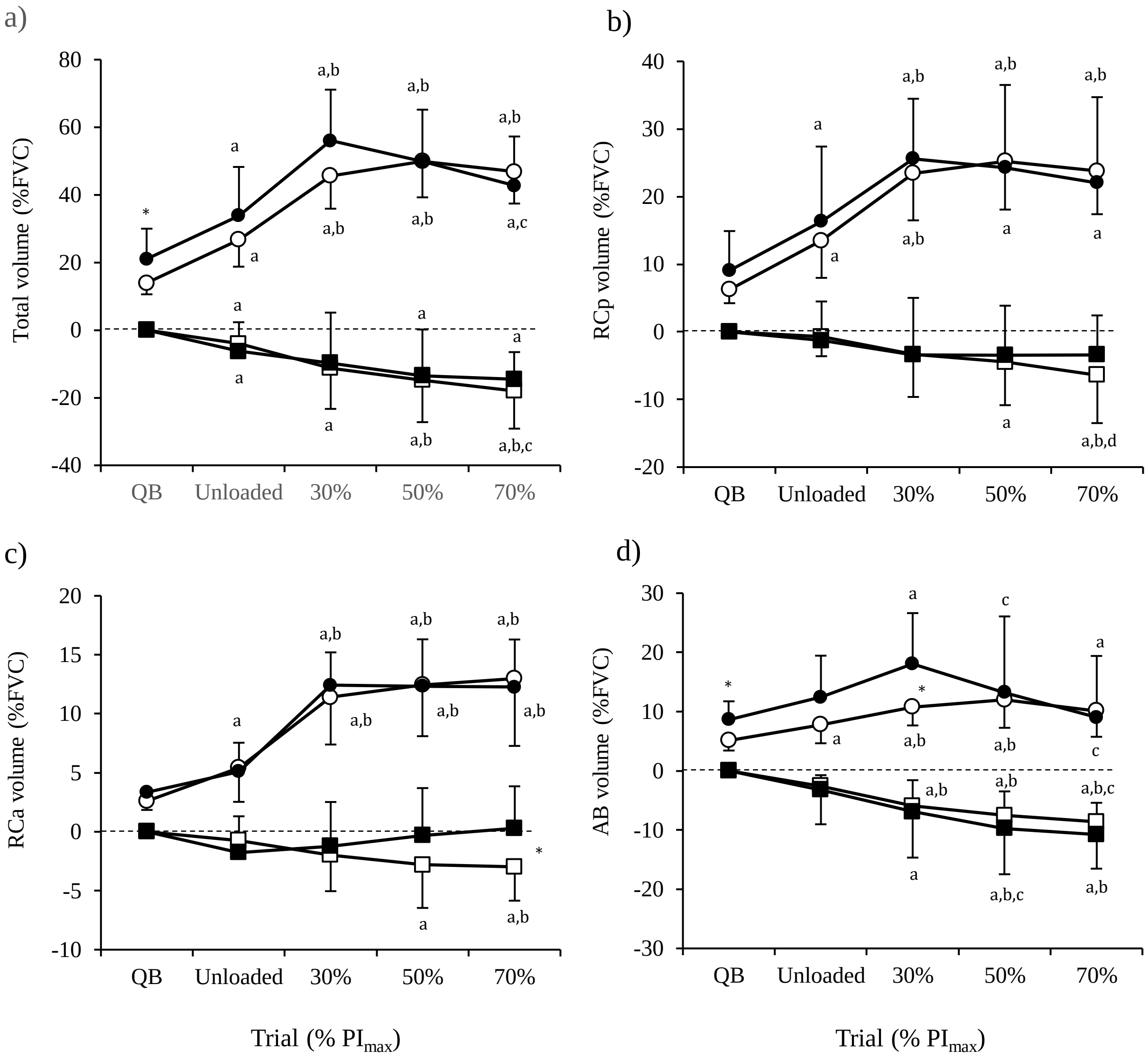


Figure 5-3. Volume changes of the a) total thoracoabdomen, b) the pulmonary rib cage (RCp), c) the abdominal rib cage (RCa) and d) the abdomen (AB) in younger (*open symbols*) and older (*closed symbols*) adults during TFRL at 10 breaths/min expressed as %FVC. *Circles* indicate end-inspiration and *squares* indicate end-expiration. *Dashed line* indicates end-expiratory volume (V_{EE}) at quiet breathing (QB). ^{a} significant difference from QB, ^{b} significant difference from unloaded, ^{c} significant difference from 30%, ^{d} significant difference from 50%, * significant difference between age groups at corresponding intensity.

5.3.3. Tidal thoracoabdominal volume changes during TFRL

Friedman tests showed significant changes across trials for the total thoracoabdominal V_T and its compartments ($V_{T,\,RCp}$, $V_{T,\,RCa}$, $V_{T,\,AB}$) along with $\dot{V}_E$, inspiratory and expiratory flow rates in both younger and older participants (all $p<0.001$). No significant changes were observed across trials for percentage contribution (%) of RCp in both younger ($p=0.468$) and older ($p=0.468$) adults. Significant increases in %RCa were observed across in both age groups (both $p<0.001$), along with significant decreases in %Ab across trials for younger ($p<0.001$) and older ($p=0.034$) adults. Specific between trial differences, assessed via the Wilcoxon test, are outlined in Table 5-2.

Importantly, between-group differences in absolute values were observed at 70% PI_{max} for total V_T ($p=0.030$), $V_{T,\,RCp}$ ($p=0.022$), $V_{T,\,RCa}$ ($p=0.009$), and $V_{T,\,AB}$ ($p=0.022$) with younger adults showing significantly higher values. Furthermore, when expressed as delta changes from QB values (Δ), younger adults showed a greater Δtotal V_T at 70% PI_{max} ($p=0.011$); $\Delta V_{T,\,RCp}$ at 50 ($p=0.047$) and 70% PI_{max} ($p=0.011$); and $\Delta V_{T,\,RCa}$ at 50 ($p=0.019$) and 70% PI_{max} ($p=0.005$), with no differences observed in $\Delta V_{T,\,AB}$ compared to older adults. Furthermore, the only observable difference in $\dot{V}_E$ between age groups was at 70% PI_{max} (and only when expressed as $\Delta\dot{V}_E$) with younger adults showing significantly higher values ($p=0.019$). Similarly, younger adults had significantly higher inspiratory flow rate values at 70% PI_{max} ($p=0.003$) only. No differences between age groups were observed at any intensity for expiratory flow rate.

Table 5-2. Changes in tidal volume of the total thoracoabdomen and its compartments, minute ventilation, and inspiratory and expiratory flow rates across trials.

	Younger adults					**Older adults**				
	QB	**Unloaded**	**30%**	**50%**	**70%**	**QB**	**Unloaded**	**30%**	**50%**	**70%**
Total V_T (L)	0.58 (0.51-0.86)	1.40 (1.26-1.66)^{a}	2.62 (2.12-3.14)^{a,b}	2.99 (2.71-3.32)^{a,b,c}	3.00 (2.46-3.32)^{a,b,c,*}	0.80 (0.64-0.93)	1.46 (1.17-1.78)^{a}	2.42 (2.02-2.83)^{a,b}	2.34 (2.18-3.01)^{a,b}	2.36 (1.87-2.58)^{a,b,*}
Δ Total V_T (L)		0.89 (0.63-1.06)^{a}	2.02 (1.64-2.36)^{a,b}	2.27 (1.95-2.80)^{a,b,c}	2.14 (1.88-2.83)^{a,b,c,*}		0.55 (0.48-0.85)^{a}	1.69 (1.03-2.21)^{a,b}	1.70 (1.30-2.19)^{a,b}	1.46 (1.15-1.80)^{a,b,*}
RCp V_T (L)	0.28 (0.25-0.33)	0.59 (0.51-0.89)^{a}	1.25 (1.01-1.49)^{a,b}	1.24 (1.05-1.71)^{a,b,c}	1.29 (1.09-1.80)^{a,b,c,*}	0.31 (0.22-0.45)	0.68 (0.52-0.76)^{a}	1.04 (0.81-1.24)^{a,b}	1.02 (0.78-1.24)^{a,b}	0.89 (0.76-1.12)^{a,b,*}
Δ RCp V_T (L)		0.37 (0.25-0.56)^{a}	0.92 (0.73-1.14)^{a,b}	0.99 (0.80-1.55)^{a,b,c,*}	1.01 (0.71-1.66)^{a,b,c,*}		0.30 (0.18-35)^{a}	0.79 (0.36-0.91)^{a,b}	0.74 (0.45-0.92)^{a,b,*}	0.59 (0.40-0.81)^{a,b,*}
RCp (%)	42.5 (37.8-52.0)	43.6 (37.5-50.9)	47.1 (43.0-52.5)	45.6 (41.7-51.0)	45.6 (43.9-52.5)	38.2 (34.6-53.2)	42.6 (37.0-49.7)	36.1 (35.2-48.4)	37.2 (35.5-54.7)	41.9 (37.3-54.6)
RCa V_T (L)	0.11 (0.08-0.17)	0.28 (0.24-0.34)^{a}	0.63 (0.42-0.79)^{a,b}	0.70 (0.60-0.94)^{a,b,c}	0.77 (0.57-0.95)^{a,b,c,*}	0.13 (0.09-0.17)	0.26 (0.16-0.31)^{a}	0.51 (0.40-0.66)^{a,b}	0.44 (0.40-0.63)^{a,b}	0.47 (0.35-0.58)^{a,b,*}
Δ RCa V_T (L)		0.19 (0.11-0.21)^{a}	0.52 (0.35-0.62)^{a,b}	0.60 (0.45-0.76)^{a,b,c,*}	0.55 (0.48-0.77)^{a,b,c,*}		0.11 (0.07-0.17)^{a}	0.42 (0.26-0.47)^{a,b}	0.36 (0.30-0.46)^{a,b,*}	0.36 (0.22-0.49)^{a,b,*}
RCa (%)	17.8 (15.4-19.3)	19.7 (17.9-22.4)^{a,*}	22.6 (19.2-26.4)^{a}	23.6 (21.3-25.9)^{a,b}	23.1 (22.6-27.5)^{a,b}	15.0 (13.4-17.8)	16.4 (14.7-18.2)*	19.7 (17.7-24.0)^{a,b}	19.5 (17.8-22.4)^{a,b}	21.9 (17.4-25.2)^{a,b}
Ab V_T (L)	0.23 (0.18-0.29)	0.48 (0.36-0.54)^{a}	0.72 (0.66-0.97)^{a,b}	0.97 (0.77-1.06)^{a,b,c}	0.96 (0.67-1.03)^{a,b}	0.36 (0.21-0.39)	0.59 (0.38-0.70)^{a}	0.93 (0.72-1.19)^{a,b}	0.88 (0.68-1.21)^{a,b}	0.85 (0.57-1.00)^{a}

ΔAb V_T (L)		0.28 (0.13-0.33)[a]	0.48 (0.40-0.64)[a,b]	0.75 (0.58-0.80)[a,b,c]	0.70 (0.49-0.84)[a,b]		0.21 (0.17-0.33)[a]	0.57 (0.34-0.88)[a,b]	0.61 (0.34-0.79)[a,b]	0.48 (0.21-0.57)[a]
Ab (%)	37.6 (32.0-41.1)	36.8 (30.9-40.7)[a]	28.3 (24.6-35.1)[a,b,*]	28.9 (25.5-33.8)[a]	30.5 (24.4-31.8)[a,b]	45.9 (33.5-50.8)	39.5 (33.9-47.7)	39.8 (35.1-45.4)[*]	38.3 (28.7-45.7)[a]	35.7 (27.0-41.1)[a,b]
$\dot{V}_E$ (L/min)	8.87 (7.54-11.08)	14.24 (12.71-16.28)[a]	26.27 (21.58-31.65)[a,b]	29.76 (27.18-33.93)[a,b,c]	30.11 (24.63-34.40)[a,b,c]	8.81 (7.12-10.46)	15.06 (11.73-17.51)[a]	24.23 (20.46-28.28)[a,b]	23.60 (22.18-30.73)[a,b]	24.05 (18.57-26.18)[a,b]
Δ $\dot{V}_E$ (L/min)		6.23 (3.45-7.21)[a]	15.24 (14.72-20.90)[a,b]	19.62 (17.87-24.47)[a,b,c]	19.38 (17.09-25.09)[a,b,c,*]		5.39 (3.82-6.61)[a]	15.86 (10.46-19.43)[a,b]	16.20 (12.72-19.34)[a,b]	14.72 (8.08-17.58)[a,b,*]
Insp flow rate (L/s)	0.40 (0.32-0.47)	0.57 (0.51-0.70)[a]	1.57 (0.98-2.09)[a,b]	1.70 (1.43-2.01)[a,b]	1.47 (1.16-2.06)[a,b,*]	0.48 (0.43-0.53)	0.62 (0.56-0.77)[a]	1.24 (1.01-1.56)[a,b]	1.26 (0.88-1.61)[a,b]	0.90 (0.77-1.05)[a,c,d,*]
Exp flow rate (L/s)	0.28 (0.22-0.33)	0.41 (0.35-0.49)[a]	0.62 (0.56-0.73)[a,b]	0.68 (0.66-0.87)[a,b,c]	0.73 (0.67-0.96)[a,b,c]	0.24 (0.19-0.32)	0.40 (0.31-0.46)[a]	0.60 (0.52-0.74)[a,b]	0.64 (0.54-0.75)[a,b]	0.65 (0.50-0.85)[a,b]

Data presented as median (IQR); QB, quiet breathing; RCP, pulmonary rib cage; RCA, abdominal rib cage; AB, abdomen; V_T, tidal volume; $\dot{V}_E$, minute ventilation; Insp, inspiratory; Exp, expiratory; L, litres; L/min, litres per minute; L/s, litres per second; Δ, delta change from QB value. [a] significant difference from QB, [b] significant difference from unloaded, [c] significant difference from 30%, * significant difference between age groups at corresponding intensity.

The V_T contribution of RC and AB compartments to the total V_T during different intensities of TFRL in young and older adults are shown in Figure 5-4. Significant correlations between RC volume and total thoracoabdominal volume were found during all intensities in both young (30%: r=0.930, p<0.001; 50%: r=0.957, p<0.001; 70%: 0.965, p<0.001) and older groups (30%: r=0.783, p=0.003; 50%: r=0.803, p=0.002; 70%: r=0.772, p=0.003). Furthermore, significant correlations were also found between AB volume and total thoracoabdominal volume during all intensities in both young (30%: r=0.725, p=0.008; 50%: r=0.625, p=0.022; 70%: 0.632, p=0.20) and older groups (30%: r=0.820, p=0.001; 50%: r=0.840, p=0.001; 70%: r=0.783, p=0.003). No significant differences between regression slopes at different intensities were observed in either group.

Regression slopes for the RC contribution were significantly greater than those of the AB contribution in younger adults at 30, 50, and 70% PI_{max} (all p<0.001). No difference in regression slopes between compartments were observed at any intensity of TFRL in the older group at (30%: p=0.701; 50%: p=0.651; 70%: p=0.925). Younger adults had significantly greater regression slopes for RC contribution to total V_T, along with lower regression slopes for abdomen contribution to total V_T compared to older adults at 30% (both p=0.034), 50% (both p=0.017), and 70% PI_{max} (both p=0.035).

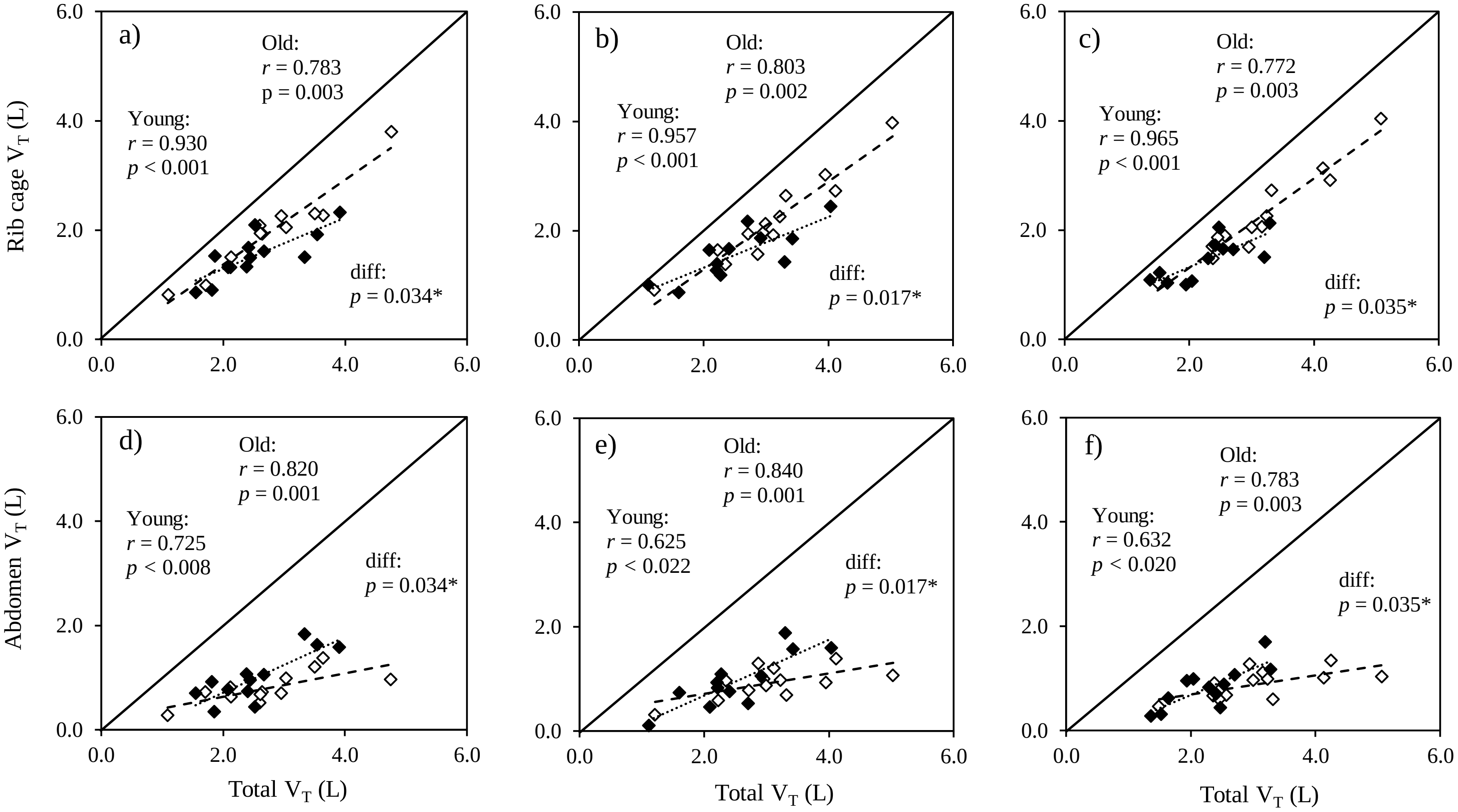


Figure 5-4. Compartmental contribution of the rib cage (*upper panels*) and abdomen (*lower panels*) in younger (*open symbols, dashed regression line*) and older adults (*closed symbols, dotted regression line*) during TFRL at 30% (*a and d*), 50% (*b and e*), and 70% PI_{max} (*c and f*). The distance from the identity lines represent contributions of the abdomen compartment (*top panels*) and rib cage compartment (*bottom panels*). Regression (*r*) and significance (*p*) values for slopes at each intensity are reported for both age groups along with the *p* values for differences in slopes between age groups. *denote significant difference between slopes.

5.3.4. Operational and tidal thoracoabdominal volume changes between protocols of TFRL

The operational thoracoabdominal volumes during subgroup TFRL at 6 breaths/min with maximised V_T are shown below and expressed as both absolute values (Figure 5-5) and %FVC (Figure 5-6). Significant changes in V_{EI} across trials were found within the total and each compartment of the thoracoabdomen in both younger and older adults when expressed as both absolute and normalised values. For the younger adults, changes were attributed to increases in V_{EI} (both within the total, and every compartment of the thoracoabdomen) from QB at each loaded intensity (Figures 5-5 and 5-6). The older group showed a similar pattern of increased V_{EI} from resting values at each intensity apart from $V_{EI,\ AB}$ at 70% (p=0.314). No significant differences in total or compartmental V_{EI} were observed between loaded intensities in either age group.

Age related differences in V_{EI} were observed at higher intensities during TFRL at 6 breaths/min with younger adults showing significantly higher total V_{EI} at 50% (p=0.039) and 70% PI_{max} (p=0.007), and $V_{EI,\ RCA}$ at 70% PI_{max} (p=0.034) compared to the older group, however, these differences disappeared when expressed as %FVC. Values for total V_{EI} were significantly higher during TFRL at 6 breaths/min compared to at 10 breaths/min within the younger group at 30% and 70% PI_{max} (both p=0.028) but not at 50% PI_{max} (p=0.063), along with higher $V_{EI,\ RCP}$ at 30% PI_{max} when expressed as %FVC only (p=0.046). For older adults, total V_{EI} was higher during 6 breaths/min at 30% PI_{max} when expressed as %FVC only (p=0.038), with the difference during this intensity attributable to a greater $V_{EI,\ RCP}$ (p=0.028) during the 6 breaths/min protocol.

Significant changes in V_{EE} across trials were observed within the total and each compartment of the thoracoabdomen for younger adults with these changes attributed to significant decreases in V_{EE} (both within the total, and every compartment of the thoracoabdomen) from

QB at each loaded intensity. For older adults, changes in V_{EE} across trials occurred within the total thoracoabdomen, RCp, and AB, but not the RCa compartment (p=0.269). These changes occurred due to decreases in V_{EE} from QB values at all intensities within the total thoaracoabdomen and AB compartment, and at 30% and 50% PI_{max} only within the RCp compartment. No significant differences in total or compartmental V_{EE} were observed between loaded intensities in either age group.

Younger adults showed significantly greater reductions in absolute total V_{EE} during TFRL at 6 breaths/min compared to their older counterparts at 50% (p=0.039) and 70% PI_{max} (p=0.050), with values at 30% PI_{max} failing to reach statistical significance (p=0.059). Furthermore, younger adults showed significantly greater reductions in absolute $V_{EE, RCP}$ at 70% PI_{max} (p=0.050) and $V_{EE, RCA}$ at 30% (p=0.045) and 50% PI_{max} (p=0.050). These age-related differences disappeared when expressed as %FVC, excluding $V_{EE, RCP}$ at 70% PI_{max} (p=0.050). Values for total V_{EE} were significantly lower within the younger group during TFRL at 6 breaths/min compared to at 10 breaths/min at 30% PI_{max} only (p=0.028) Furthermore, significantly lower values were observed for $V_{EE, RCP}$ at 30% (p=0.028) and 50% PI_{max} (p=0.018), $V_{EE, RCA}$ at 30% (p=0.046), and $V_{EE, AB}$ at 50% PI_{max} (p=0.028). For older adults, significantly lower values for total V_{EE} during the 6 breaths/min protocol compared to 10 breaths/min were observed during 70% PI_{max} only (p=0.015), and were attributable to lower $V_{EE, RCA}$ (p=0.050). When these values were normalised for lung size (%FVC), total V_{EE} remained significantly lower (p=0.038) but the significance between protocols for $V_{EE, RCA}$ at 70% PI_{max} disappeared (p=0.066).

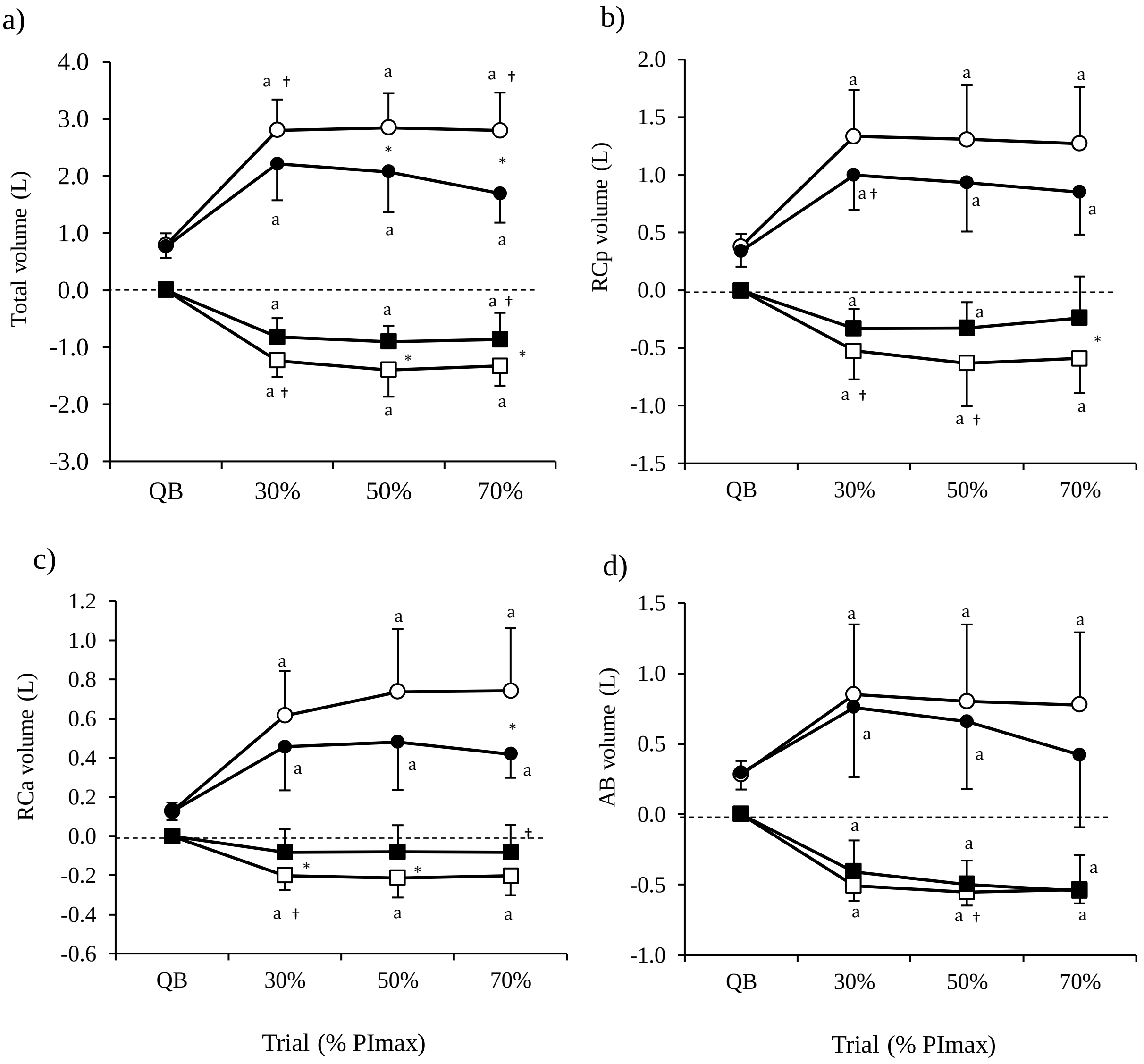


Figure 5-5. Volume changes of the a) total thoracoabdomen, b) the pulmonary rib cage (RCp), c) the abdominal rib cage (RCa) and d) the abdomen (AB) in younger (*open symbols*) and older (*closed symbols*) adults during TFRL at 6 breaths/min expressed as absolute values (L). *Circles* indicate end-inspiration and *squares* indicate end-expiration. *Dashed line* indicates end-expiratory volume (V_{EE}) at quiet breathing (QB). ^{a} significant difference from QB, ^{b} significant difference from 30%, ^{d} significant difference from 50%, * significant difference between age groups at corresponding intensity, † significant difference between TFRL protocols.

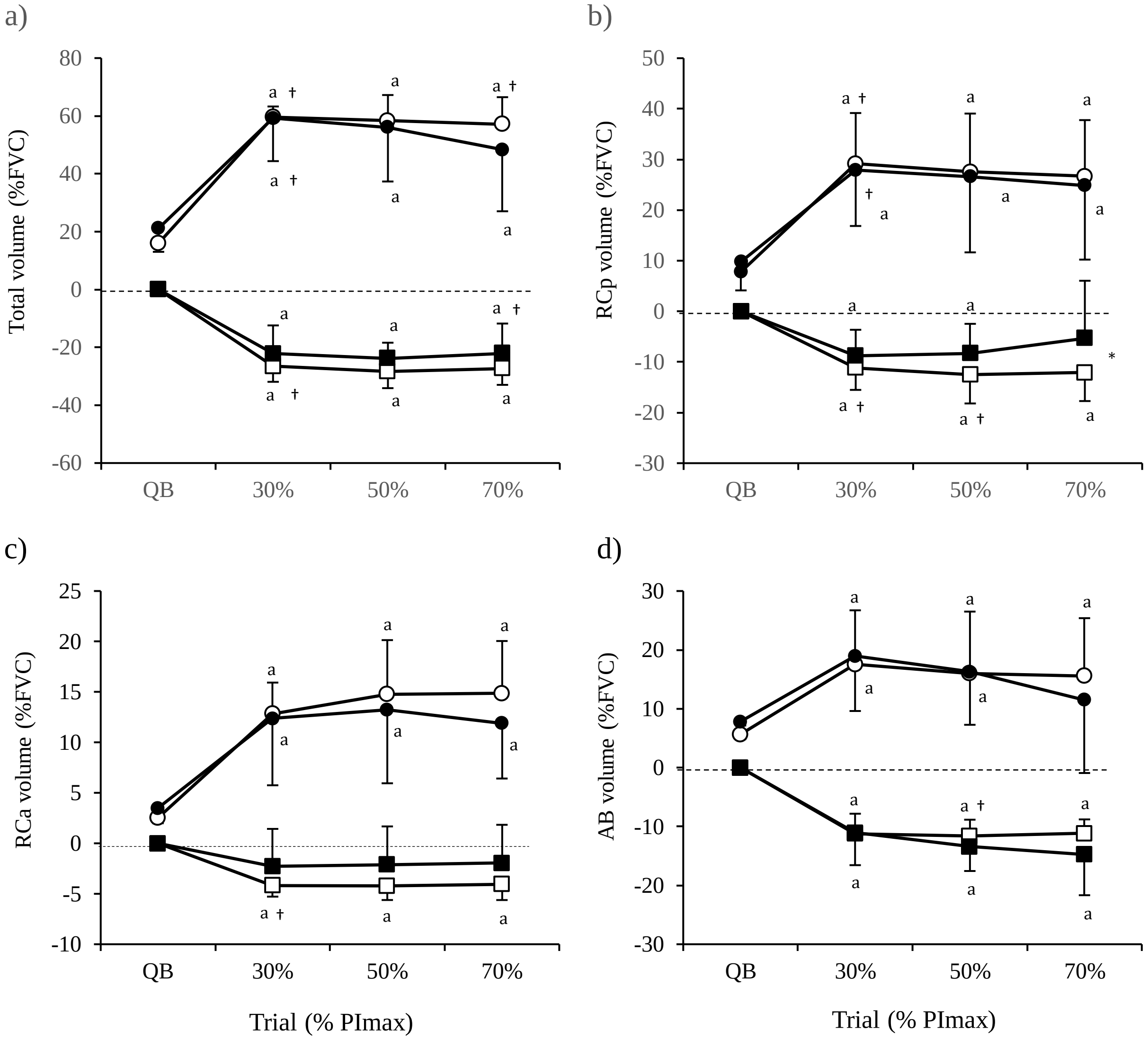


Figure 5-6. Volume changes of the a) total thoracoabdomen, b) the pulmonary rib cage (RCp), c) the abdominal rib cage (RCa), and d) the abdomen (AB) in younger (*open symbols*) and older (*closed symbols*) adults during TFRL at 6 breaths/min expressed as %FVC. *Circles* indicate end-inspiration and *squares* indicate end-expiration *Dashed line* indicates end-expiratory volume (V_{EE}) at quiet breathing (QB). ^{a} significant difference from QB, ^{b} significant difference from 30%, ^{d} significant difference from 50%, * significant difference between age groups at corresponding intensity, † significant difference between TFRL protocols.

Subgroup analysis of V_T changes in the thoracoabdomen and its compartments during TFRL at 6 breaths/min with maximum V_T compared to during TFRL at 10 breaths/min are shown below (younger adults: Table 5-3a; older adults: Table 5-3b).

Significantly greater absolute total V_T at all TFRL intensities (30%: p=0.028; 50%: p=0.018; 70%: p=0.043) during the 6 breaths/min protocol compared to 10 breaths/min within the younger subgroup were attributable to significantly greater $V_{T, AB}$ at all intensities, $V_{T, RCp}$ at 30% and 50% PI_{max}, and $V_{T, RCa}$ at 30% PI_{max} only. Delta (Δ) values at 70% PI_{max}, however, did not differ between protocols within the younger group. For the older subgroup, total V_T was significantly greater during the 6 breaths/min protocol compared to 10 breaths/min at 30% and 50% PI_{max} (p=0.008 and p=0.025 respectively) but not at 70% PI_{max} (p=0.139). This was attributable to significantly greater (absolute and Δ) $V_{T, RCp}$ at 30% (both p=0.008) and 50% PI_{max} (both p=0.017) and $V_{T, AB}$ at 30% PI_{max} only (absolute: p=0.021; Δ: p=0.013).

The younger subgroup had significantly greater total V_T during the 6 breaths/min protocol all intensities of TFRL compared to the older subgroup (30%: p=0.025; 50%: p=0.013; 70%: 0.001). Specifically, the younger subgroup had greater $V_{T, RCp}$ at all intensities, and greater $V_{T, RCa}$ at 50% and 70% PI_{max}. No significant difference within the $V_{T, AB}$ compartment were observed between age groups at any intensity of TFRL at 6 breaths/min.

Table 5-3a. Changes in tidal volume of the total thoracoabdomen and its compartments, minute ventilation, and inspiratory and expiratory flow rates during TFRL at 10 breaths/min and 6 breaths/min in younger adults.

	Younger adults							
	10 breaths/min				**6 breaths/min**			
	QB	**30%**	**50%**	**70%**	**QB**	**30%**	**50%**	**70%**
Total V_T (L)	0.83 (0.60-0.94)	2.64 (2.35-3.29)^{a,†}	2.99 (2.91-3.63)^{a,*,†}	3.16 (2.76-3.73)^{a,*,†}	0.80 (0.68-0.90)	4.03 (3.75-4.43)^{a,*,†}	4.38 (3.81-4.79)^{a,*,†}	4.17 (3.82-4.66)^{a,*,†}
ΔTotal V_T (L)		1.97 (1.63-2.52)^{a,†}	2.27 (1.98-2.89)^{a,*,†}	2.48 (1.96-2.98)^{a,*}		3.31 (3.12-3.60)^{a,*,†}	3.53 (3.18-3.85)^{a,*,†}	3.32 (3.19-3.78)^{a,*}
RCp V_T (L)	0.33 (0.30-0.42)	1.14 (1.06-1.56)^{a,†}	1.24 (1.01-2.05)^{a,†}	1.13 (1.02-2.14)^{a,*}	0.36 (0.31-0.42)	1.86 (1.59-2.18)^{a,*,†}	1.93 (1.60-2.46)^{a,*,†}	2.10 (1.60-2.18)^{a,*}
ΔRCp V_T (L)		0.87 (0.73-1.13)^{a,†}	0.83 (0.75-1.62)^{a,†}	0.84 (0.70-1.71)^{a,*}		1.47 (1.27-1.85)^{a,*,†}	1.52 (1.27-2.03)^{a,*,†}	1.69 (1.27-1.81)^{a,*}
RCa V_T (L)	0.17 (0.12-0.19)	0.77 (0.39-0.95)^{a,†}	0.88 (0.61-0.96)^{a,*}	0.80 (0.69-1.02)^{a,*}	0.13 (0.10-0.16)	0.75 (0.59-1.04)^{a,†}	1.10 (0.62-1.22)^{a,*}	1.06 (0.68-1.18)^{a,*}
Δ RCa V_T (L)		0.55 (0.32-0.77)^{a,†}	0.65 (0.49-0.79)^{a,*}	0.64 (0.54-0.85)^{a,*}		0.61 (0.52-0.91)^{a,*,†}	0.92 (0.53-1.07)^{a,*}	0.92 (0.59-1.00)^{a,*}
Ab V_T (L)	0.25 (0.20-0.31)	0.72 (0.70-0.88)^{a,†}	0.97 (0.90-1.03)^{a,†}	1.01 (0.79-1.07)^{a,†}	0.33 (0.21-0.35)	1.34 (1.01-1.60)^{a,†}	1.22 (1.03-1.48)^{a,†}	1.22 (1.00-1.40)^{a,†}
ΔAb V_T (L)		0.42 (0.39-0.68)^{a,†}	0.75 (0.62-0.81)^{a,†}	0.73 (0.59-0.84)^{a,†}		1.06 (0.83-1.27)^{a,†}	0.99 (0.80-1.13)^{a,†}	0.99 (0.75-1.05)^{a,†}
$\dot{V}_E$ (L/min)	10.35 (9.03-11.13)	26.28 (23.76-32.99)^{a}	29.76 (28.98-36.86)^{a,*}	32.10 (27.80-37.88)^{a,*,†}	10.09 (8.91-12.47)	24.30 (23.05-26.76)^{a,*}	27.15 (23.49-28.60)^{a}	24.79 (23.72-28.66)^{a,†}
Δ $\dot{V}_E$ (L/min)		15.20 (15.07-21.36)^{a}	20.55 (18.22-24.29)^{a}	22.91 (18.47-25.31)^{a,*,†}		13.60 (10.38-15.32)^{a}	13.91 (11.29-18.93)^{a}	14.68 (10.86-17.49)^{a,*,†}

Insp flow rate (L/s)	0.42 (0.38-0.48)	1.50 (1.18-2.15)[a]	1.70 (1.59-1.98)[a,*]	1.55 (1.33-1.92)[a,*]	0.43 (0.38-0.55)	1.42 (1.31-1.93)[a,*]	1.57 (1.46-1.65)[a,*]	1.34 (1.20-1.82)[a,*]
Exp flow rate (L/s)	0.31 (0.29-0.34)	0.63 (0.59-0.75)[a]	0.73 (0.67-0.88)[a]	0.88 (0.67-1.04)[a]	0.34 (0.25-0.35)	0.57 (0.49-0.63)[a]	0.63 (0.54-0.66)[a]	0.63 (0.58-0.65)[a,*,†]

Data presented as median (IQR); QB, quiet breathing; RCP, pulmonary rib cage; RCA, abdominal rib cage; AB, abdomen; V_T, tidal volume; $\dot{V}_E$, minute ventilation; Insp, inspiratory; Exp, expiratory; L, litres; L/min, litres per minute; L/s, litres per second; Δ, delta change from QB value. [a] significant difference from QB, [b] significant difference from 30%, [c] significant difference from 50%, * significant difference between age groups at corresponding intensity (see Table 5-3b), [†] significant difference between TFRL protocols.

Table 5-3b. Changes in tidal volume of the total thoracoabdomen and its compartments, minute ventilation, and inspiratory and expiratory flow rates during TFRL at 10 breaths/min and 6 breaths/min in older adults.

	Older adults							
	10 breaths/min				**6 breaths/min**			
	QB	**30%**	**50%**	**70%**	**QB**	**30%**	**50%**	**70%**
Total V_T (L)	0.76 (0.64-0.87)	2.44 (1.86-2.67)[a,†]	2.27 (2.09-2.70)[a,*,†]	2.04 (1.64-2.47)[a,*]	0.85 (0.68-0.87)	2.83 (2.51-3.15)[a,*,†]	2.96 (2.55-3.30)[a,*,†]	2.48 (2.41-2.68)[a,*]
ΔTotal V_T (L)		1.68 (1.06-2.06)[a,†]	1.57 (1.19-2.06)[a,*,†]	1.28 (1.01-1.67)[a,*]		2.18 (1.89-2.29)[a,*,†]	2.15 (1.73-2.46)[a,*,†]	1.68 (1.53-2.03)[a,*]
RCp V_T (L)	0.34 (0.24-0.43)	1.09 (0.87-1.24)[a,†]	0.96 (0.77-1.23)[a,†]	0.84 (0.72-1.04)[a,*]	0.35 (0.28-0.45)	1.27 (1.09-1.64)[a,*,†]	1.15 (1.03-1.45)[a,*,†]	1.16 (0.84-1.27)[a,*]
ΔRCp V_T (L)		0.77 (0.37-0.88)[a,†]	0.70 (0.45-0.82)[a,†]	0.46 (0.38-0.77)[a,*]		0.99 (0.71-1.15)[a,*,†]	0.84 (0.72-1.16)[a,*,†]	0.81 (0.56-0.89)[a,*]
RCa V_T (L)	0.13 (0.09-0.14)	0.50 (0.42-0.62)[a]	0.42 (0.37-0.48)[a,*]	0.37 (0.32-0.56)[a,*]	0.13 (0.10-0.15)	0.51 (0.42-0.59)[a,*]	0.50 (0.47-0.63)[a,*]	0.51 (0.41-0.53)[a,*]
Δ RCa V_T (L)		0.41 (0.26-0.47)[a]	0.32 (0.25-0.39)[a,*]	0.23 (0.22-0.38)[a,*]		0.37 (0.30-0.45)[a,*]	0.38 (0.36-0.50)[a,*]	0.36 (0.33-0.42)[a,*]
Ab V_T (L)	0.36 (0.21-0.38)	0.91 (0.69-1.06)[a,†]	0.75 (0.53-1.09)[a]	0.70 (0.43-0.95)[a]	0.30 (0.21-0.37)	1.13 (0.82-1.53)[a,†]	0.85 (0.77-1.58)[a]	0.98 (0.61-1.18)[a]
ΔAb V_T (L)		0.56 (0.31-0.85)[a,†]	0.58 (0.31-0.72)[a]	0.52 (0.21-0.56)[a]		0.68 (0.55-1.17)[a,†]	0.62 (0.55-1.22)[a]	0.68 (0.43-0.79)[a]
$\dot{V}_E$ (L/min)	8.21 (7.15-8.75)	24.45 (19.74-26.5)[a,†]	22.51 (22.01-27.27)[a,*,†]	20.62 (16.43-25.69)[a,*,†]	8.48 (7.16-10.14)	17.15 (15.22-20.63)[a,*,†]	18.40 (15.34-20.19)[a,†]	15.31 (14.67-16.44)[a,†]
Δ $\dot{V}_E$ (L/min)		16.81 (11.06-19.35)[a,†]	15.59 (13.56-18.60)[a,†]	12.41 (9..28-17.52)[a,*,†]		9.03 (8.04-10.88)[a,†]	8.27 (6.98-12.17)[a,†]	7.80 (4.92-8.32)[a,*,†]

Insp flow rate (L/s)	0.46 (0.44-0.52)	1.21 (0.87-1.40)[a]	1.05 (0.88-1.40)[a,*]	0.87 (0.74-0.91)[a,b,c,*]	0.46 (0.43-0.47)	1.04 (0.78-1.09)[a,*]	0.90 (0.61-1.32)[a,*]	0.72 (0.70-0.82)[a,*]
Exp flow rate (L/s)	0.24 (0.19-0.25)	0.60 (0.58-0.71)[a,†]	0.64 (0.56-0.69)[a,†]	0.65 (0.49-0.81)[a,†]	0.22 (0.20-0.31)	0.45 (0.39-0.63)[a,†]	0.46 (0.43-0.51)[a,†]	0.40 (0.38-0.43)[a,c,*,†]

Data presented as median (IQR); QB, quiet breathing; RCP, pulmonary rib cage; RCA, abdominal rib cage; AB, abdomen; V_T, tidal volume; $\dot{V}_E$, minute ventilation; Insp, inspiratory; Exp, expiratory; L, litres; L/min, litres per minute; L/s, litres per second; Δ, delta change from QB value. [a] significant difference from QB, [b] significant difference from 30%, [c] significant difference from 50%, * significant difference between age groups at corresponding intensity (see Table 5-3a), [†] significant difference between TFRL protocol

5.3.5. Gas exchange responses to inspiratory muscle loading

No significant group x trial interaction was observed for partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$; p=0.742, F=0.492) or partial pressure of end-tidal oxygen ($P_{ET}O_2$; p=0.108, F=2.335). A significant change over TFRL trials were observed in both $P_{ET}CO_2$ (p<0.001, F=68.969) and $P_{ET}O_2$ (p<0.001, F=26.609). Values for $P_{ET}CO_2$ significantly decreased from both QB and unloaded breathing levels during all subsequent trials in both age groups. No significant differences were observed between age groups at each intensity.

For $P_{ET}O_2$, values significantly increased from QB during all intensities of loaded breathing in both age groups. $P_{ET}O_2$ was significantly higher compared to QB values during the unloaded trial in older (p<0.001) but not younger (p=0.070) adults. Values were significantly higher at 30% and 50% compared to unloaded values in the younger group only (p=0.014 and p=0.025, respectively) with no differences between loaded trials in either group. No significant differences were observed between age groups at each intensity.

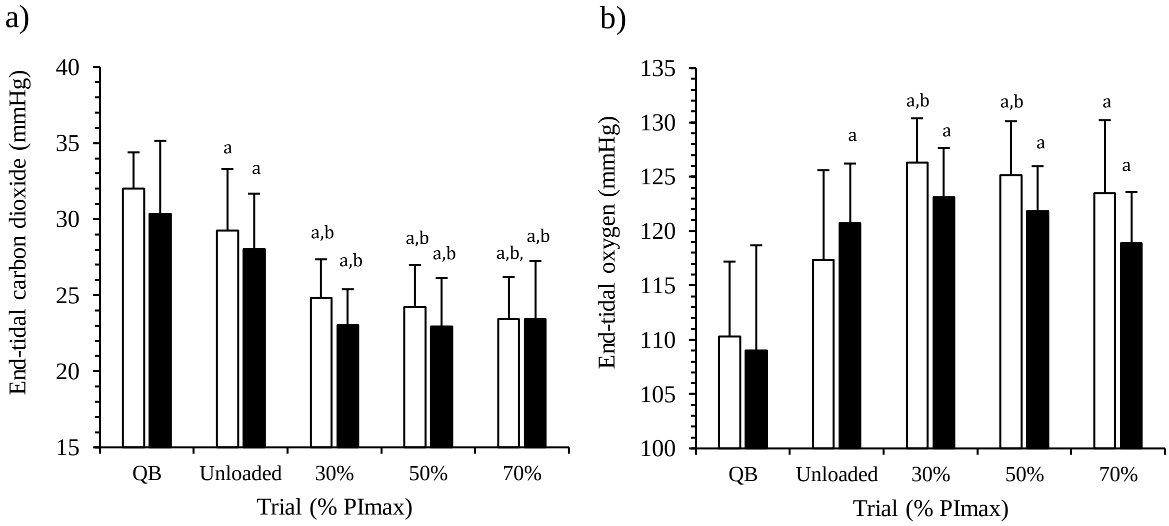


Figure 5-7. Partial pressure of end-tidal (P_{ET}) changes in a) carbon dioxide (CO_2) and b) oxygen (O_2) in younger (*open bars*) and older (*closed bars*). ^{a} significant difference from QB, ^{b} significant difference from unloaded, ^{c} significant difference from 30%, ^{d} significant difference from 50%, * significant difference between age groups at corresponding intensity.

Subgroup analysis of P_{ET} responses during TFRL at 6 breaths/min with maximum V_T compared to TFRL at 10 breaths/min with no specific instructions relating to V_T are shown in Table 5-4. Two-way repeated measures ANOVA revealed significant interactions for protocol x trial for both $P_{ET}CO_2$ ($p<0.001$, F=29.120) and $P_{ET}O_2$ ($p<0.001$, F=33.023) but no significant interaction for protocol x trial x group ($P_{ET}CO_2$: p=0.510, F=0.785; $P_{ET}O_2$: p=0.873, F=0.233). When compared to TFRL at 10 breaths/min with no specific instructions relating to V_T, $P_{ET}CO_2$ was significantly higher, and $P_{ET}O_2$ was significantly lower at each loaded intensity during TFRL at 6 breaths/min in both age groups (all $p\leq0.001$). No significant differences were observed between age groups.

Table 5-4. Changes in $P_{ET}CO_2$ and $P_{ET}O_2$ in younger and older adults during TFRL at 10 breaths/min and 6 breaths/min.

	Younger adults (n=7)				**Older adults (n=9)**			
	QB	**30%**	**50%**	**70%**	**QB**	**30%**	**50%**	**70%**
$P_{ET}CO_2$ (10 breaths/min)	31.98±2.72	24.66±2.77^{a,†}	24.25±2.88^{a,†}	23.76±2.67^{a,†}	30.63±4.36	22.48±1.71^{a,†}	22.73±3.64^{a,†}	23.62±4.41^{a,†}
$P_{ET}CO_2$ (6 breaths/min)		28.21±1.83^{a,†}	27.61±2.70^{a,†}	28.00±3.70^{a,†}		26.16±3.63^{a,†}	25.85±3.24^{a,†}	25.87±3.73^{a,†}
$P_{ET}O_2$ (10 breaths/min)	110.20±7.99	125.95±2.59^{a,†}	123.76±2.20^{a,†}	120.72±4.36^{a,†}	107.84±7.11	125.53±1.92^{a,†}	122.79±4.26^{a,†}	119.69±5.16^{a,†}
$P_{ET}O_2$ (6 breaths/min)		119.26±2.63^{a,†}	116.73±2.82^{b,†}	114.34±3.80^{b,†}		120.01±3.17^{a,†}	117.78±3.32^{a,b,†}	114.60±5.87^{b,†}

Data presented as mean±SD; QB, quiet breathing, $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; $P_{ET}O_2$, partial pressure of end-tidal oxygen; ^{a} significant difference from QB, ^{b} significant difference from 30%, ^{c} significant difference from 50%, * significant difference between age groups at corresponding intensity, † significant difference between TFRL protocols.

5.3.6. Respiratory effort ratings during TFRL

Two-way ANOVA revealed a significant change in Borg scale ratings for respiratory effort between trials ($p<0.001$, $F=110.306$) but no significant group x trial interaction ($p=0.537$, $F=0.538$; Figure 5-8). In both age groups, respiratory effort significantly increased from 30% to 50%, 30% to 70%, and 50% to 70% PI_{max} (all $p<0.001$). No significant difference was observed between age groups at 30 ($p=0.195$), 50% ($p=0.525$), or 70% PImax ($p=0.186$).

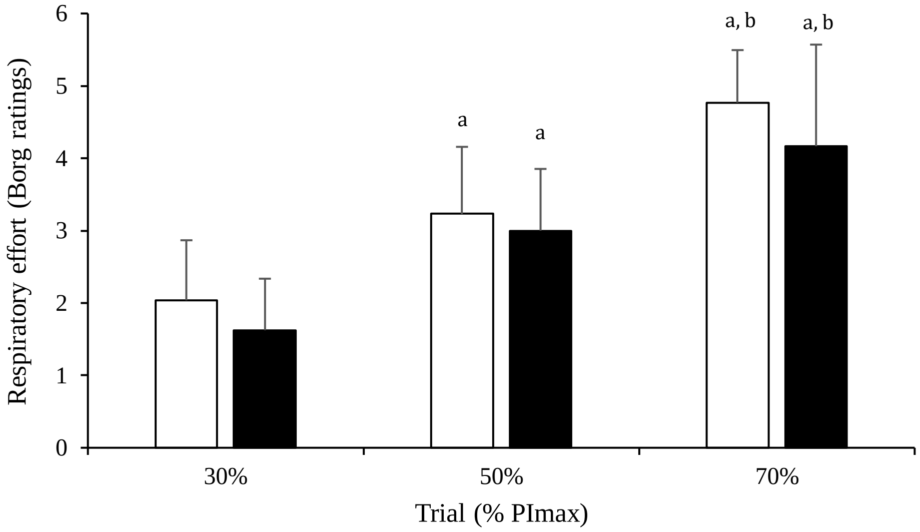


Figure 5-8. Ratings of respiratory effort across TFRL intensities in younger (*open bars*) and older (*closed bars*) adults. ^{a} significant difference from 30%, ^{b} significant difference from 50%, * significant difference between age groups at corresponding intensity.

Within the subgroups that performed TFRL at 6 breaths/min with maximum V_T, a significant interaction was found for protocol x trial ($p=0.002$, $F=10.256$) but not protocol x trial x group ($p=0.627$, $F=0.485$; Figure 5-9). Significant increases in respiratory effort ratings were observed between 30% and 50% PI_{max} during TFRL at 10 breaths/min in both young ($p=0.021$) and older adults ($p=0.001$) but not during TFRL at 6 breaths/min between (young: $p=0.293$; older: $p=0.102$). Furthermore, in older adults, respiratory effort ratings were significantly increased at 70% compared to 30% ($p<0.001$) and 50% PI_{max} ($p=0.006$) during 10 breaths/min, with significance only observed between 70% and 30% (p=0.005) and not 70% and 50% (p=0.099) during 6 breaths/min. Respiratory effort ratings were similar to those at 10 breaths/min during 30% PI_{max} for both younger (p=0.098) and older (p=1.000) individuals. During 50% PI_{max}, ratings were significantly reduced at 6 breaths/min for the younger (p=0.030) and older groups (p=0.023). Furthermore, significantly lower ratings were reported when breathing at 6 breaths/min compared to 10 breaths/min during loading at 70% PI_{max} in both younger and older adults (both p=0.001).

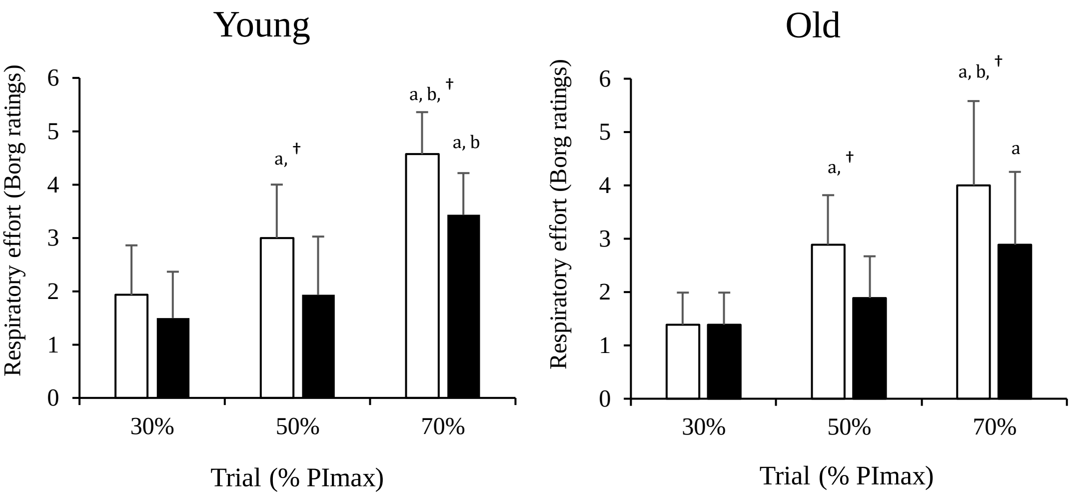


Figure 5-9. Ratings of respiratory effort across TFRL intensities during 10 breaths/min (*open bars*) and 6 breaths/min (*closed bars*) in younger (*left panel*) and older (*right panel*) adults. ^{a} significant difference from 30%, ^{b} significant difference from 50%, * significant difference between age groups at corresponding intensity, † significant difference between TFRL protocols.

5.4. Discussion

TFRL at low, moderate, and high intensities (i.e., 30, 50, and 70% PI_{max}) resulted in significant increases in total V_{EI} and significant decreases in total V_{EE} from resting levels in both younger and older adults. The main age-related differences in thoracoabdominal volume regulation during TFRL occurred within the rib cage compartments (RCp and RCa) at high intensities, with significantly higher absolute V_T and ΔV_T being observed within these compartments in the younger group. Furthermore, younger adults had significantly greater association between total V_T expansion and RC V_T expansion compared to older adults. Significant increases in $\dot{V}_E$, inspiratory and expiratory flow rates, $P_{ET}O_2$, and respiratory effort ratings, along with significant decreases in $P_{ET}CO_2$ were also observed across intensities in both age groups. The two subgroups of older and younger adults that also performed TFRL at 6 breaths/min with maximum V_T expansion showed significant reductions in $P_{ET}O_2$, and respiratory effort scores at higher intensities, along with increased $P_{ET}CO_2$ compared to TFRL at 10 breaths/min with no instructions given relating to V_T.

5.4.1. Operational thoracoabdominal volume regulation

The increased V_T during each intensity of TFRL occurred due to increases in V_{EI} and decreases in V_{EE} in both age groups. An increase in V_{EI} within RCp ($V_{RCp,\,EI}$) compartment reflects an increased activity of the rib cage muscles such as external intercostals, whilst increases in V_{EI} of the RCa ($V_{RCa,\,EI}$) and AB ($V_{AB,\,EI}$) primarily reflects greater work of the diaphragm (Aliverti et al., 1997; Chihara, Kenyon, & Macklem, 1996). Decreased $V_{RCp,\,EE}$ and $V_{RCa,\,EE}$ compartments reflects increased work of the internal intercostal muscles, and decreased $V_{AB,\,EE}$ reflects increased activity of muscles of the abdominal wall (Dellacà et al., 2001). In the present study, younger and older adults showed similar thoracoabdominal volume regulation during TFRL. Increases in total V_{EI} were predominantly due to increases in V_{EI} RC volumes and decreases in total V_{EE} volume were predominantly due to decreases in V_{EE} AB volumes, similar to responses observed during exercise in healthy individuals (Aliverti et al., 1997; Iandelli et al., 2002).

These findings are in line with previous research investigating operational thoracoabdominal volumes during TFRL in healthy adults (da Fonsêca et al., 2019) and mouth-breathing children (da Fonsêca et al., 2022; da Fonsêca et al., 2020). The authors found significant increases in $V_{RCp,\,EI}$ and $V_{RCa,\,EI}$ and observed increased EMG activity in the sternocleidomastoid, scalene and intercostal muscles during inspiratory muscle loading at both 20% and 40% PI_{max} in healthy adults compared to QB (da Fonsêca et al., 2019). These findings outline the importance of the rib cage muscles in increasing V_T expansion during TFRL, with the results from the present study expanding on the work by da Fonseca et al. (2019; 2020; 2022) by observing a similar volume regulation at higher intensities of TFRL (50% and 70% PI_{max}). da Fonsêca et al. (2019) also observed significant decreases in $V_{AB, EE}$ during inspiratory muscle loading at 20% and 40% PI_{max}. The authors suggested that the decreased $V_{AB, EE}$ occurring alongside constant $V_{RC, EE}$ was a mechanism which supported diaphragmatic contraction by increasing the muscle's pre-inspiratory length and preventing excessive shortening (Aliverti et al., 1997).

In the younger adults, $V_{AB, EE}$ was significantly decreased at all TFRL intensities, whereas $V_{RCp, EE}$ and $V_{RCa, EE}$ was significantly decreased at higher intensities of 50% and 70% PI_{max}. These findings suggest that the muscles of the abdominal wall predominantly contributed to reduce V_{EE}, however, as the inspiratory load was increased, expiratory muscles of the rib cage (i.e., internal intercostals) also become activated to help further decrease V_{EE}, thus expanding V_T. Furthermore, expiratory flow rate was also increased from QB with increasing inspiratory muscle loading also reflecting increased abdominal muscle recruitment (Martin et al., 1982). In older adults, however, decreased total V_{EE} was due to decreased $V_{AB, EE}$ only, with no significant change in $V_{RC, EE}$. The lower capacity to decrease $V_{RC, EE}$ in the older group compared to the younger group can be explained by reduced elastic recoil of the lung (Anthonisen, Danson, Robertson, & Ross, 1969; Frank et al., 1957) and reduced compliance of the chest wall (DeLorey & Babb, 1999; Rizzato & Marazzini, 1970) during the ageing process. Rizzato and Marazzini (1970) concluded that the reduced mobility of the rib cage in older adults was more apparent during expiration of expiratory reserve volume that during inspiration of IC which may explain why both age groups had similar increases in RC V_{EI}.

The present study supports previous research in that when ventilatory demand is increased, abdominal muscle recruitment during expiration is the main reason V_{EE} is reduced below FRC in healthy people (Aliverti et al., 1997; Iandelli et al., 2002). Thus, it is likely that, if participants were unable to generate enough inspiratory pressure to overcome the initial threshold to open the valve of the training device at high inspiratory muscle loaded intensities during the fixed two seconds of inspiration for each breath, then their expiratory muscles of both the abdominal wall and the RC compartments contributed to increase V_T by reducing V_{EE}. An inability to overcome the initial threshold at high intensities may explain the significant decrease in total V_{EI} from 30% PI_{max} to 70% PI_{max} in the older group. Furthermore, it is well understood that reduced FRC will lengthen diaphragmatic fibres placing them at a more favourable length-tension relationship so they can produce more pressure for a given neural output (Kikuchi et al., 1991; Martin et al., 1982). In turn, this will protect the diaphragm against contractile fatigue and improve diaphragmatic neuromechanical coupling (Laghi et al., 2014). This active contraction of abdominal muscles will store elastic energy, meaning that part of the subsequent inspiration is achieved with less activation of inspiratory muscles, thus enhancing the abdominal muscles ability to act as accessory inspiratory muscles by assisting the diaphragm and reducing inspiratory muscle work (Kikuchi et al., 1991). Kikuchi et al. (1991) also suggested that reduced FRC during inspiratory muscle loading may be due to behavioural control to minimise the sensation of dyspnoea and increase inspiratory muscle endurance.

5.4.2. Compartmental thoracoabdominal tidal volumes and contribution

Significantly lower V_T expansion of RC compartments (RCp and RCa) within the older group, both during higher intensities (50% and 70% PI_{max}) of TFRL at 10 breaths/min, and during all intensities of TFRL at 6 breaths/min with maximum V_T, were observed when compared to the younger group. Furthermore, no significant differences were observed in V_T expansion of the AB compartment between age groups during TFRL at both 10 or 6 breaths/min. These findings were further highlighted within the correlation analysis of this chapter. Both groups showed significant associations for both RC and AB contribution to total V_T during all intensities of

TFRL, implying that this method of training targets a range of respiratory muscle groups. Significantly greater regression slopes for the RC contribution to total V_T compared to those for the AB contribution to total V_T were observed within the younger group only, with no differences found between compartment contribution within the older group. This finding suggests that muscles of the rib cage are predominantly recruited during TFRL in younger adults, whereas rib cage and abdominal muscles are similarly recruited in older adults. Furthermore, younger adults had significantly greater regression slopes for RC contribution, and significantly lower slopes for AB contribution, to total V_T at all levels of TFRL compared to their older counterparts.

These findings are in line with previous studies that have utilised OEP, or similar motion capture techniques, to determine age-related changes in thoracoabdominal kinematics (de Souza et al., 2016; Mendes et al., 2020; Rodrigues et al., 2021). Mendes et al. (2020) observed a 0.20% reduction in $\%V_{T,\ RCp}$ and 0.08% reduction in $\%V_{T,\ RCa}$ for each year of increase in age between 21 and 85 years. This decrease in RC volume contribution was compensated by an average increase in 0.29% in $\%V_{T,\ AB}$ (Mendes et al., 2020), and, according to the authors, may explain the absence of influence of age on total thoracoabdominal volume (total V_T) reported in previous studies (Britto, Zampa, De Oliveira, Prado, & Parreira, 2009; Parreira et al., 2010; Verschakelen & Demedts, 1995). Rodrigues et al. (2021) investigated the feasibility to distinguish different age groups from variables of thoracoabdominal motion in physically active women but found they were unable to do so. Furthermore, the authors stated that age itself was unable to predict changes in breathing motion pattern. It was suggested that, when investigating the effects of ageing on thoracoabdominal motion, other factors including physical conditioning, time of physical activity practice, health and lifestyle conditions should be taken into account due to the multifactorial causes of age-related respiratory changes (Rodrigues et al., 2021). Similar to the findings of Mendes et al. (2020), a decreased superior thorax contribution was observed during QB and vital capacity manoeuvres with ageing, along with a compensatory increase in AB contribution was reported by Rodrigues et al. (2021). It should be noted that, in the present study, no significant differences were observed between V_T or percentage contribution of any thoracoabdominal compartments at QB, with differences only arising during inspiratory muscle loading.

Age-related differences in thoracoabdominal volume regulation during inspiratory muscle loading (specifically pressure-threshold loading) have previously been investigated (de Souza et al., 2016). During moderate inspiratory loading at 40% PI_{max}, the authors reported a predominant percentage contribution of the RCp compartment in younger adults, however, in older adults the RCp and AB contribution was similar. In the present study, the percentage contribution of the thoracoabdominal compartments during TFRL intensities were similar between age groups, apart from a significantly higher percentage AB contribution in older adults at 30% PI_{max}. The association between RC V_T expansion and total V_T expansion in the younger adults was significantly greater than the association between AB V_T expansion and total V_T expansion, which was not the case for the older adults, supporting the findings of de Souza et al. (2016). Furthermore, as with the findings from de Souza et al. (2016), the AB contribution decreased from resting levels during inspiratory loading in both young and older participants. However, the finding that pulmonary RC contribution increased during increasing inspiratory loading (de Souza et al., 2016) was not observed in the present study, with values during TFRL remaining unchanged from QB in both age groups. An increased contribution of the RCa, however, was observed at all intensities of TFRL compared to resting values in both age groups in the present study, with this variable increasing during moderate inspiratory resistance but decreasing during a PI_{max} manoeuvre in the study conducted by de Souza et al. (2016).

An explanation for the difference in thoracoabdominal compartment contribution during inspiratory muscle loading between values within the present study and those reported by de Souza et al. (2016) is likely due to the different method of inspiratory muscle loading. The application of TFRL in the present study resulted in higher V_T and $\dot{V}_E$ (~2.5–3.0 L and 25–30 L/min respectively) compared to values reported in de Souza et al. (2016) participants who used pressure-threshold loading (~0.9–1.3 L and ~11–15 L/min respectively). A recent study has reported significantly greater V_T in children with mouth-breathing syndrome during TFRL compared to pressure-threshold loading at 20% and 40% PI_{max} (da Fonsêca et al., 2022). It is likely that participants within de Souza and colleagues study experienced an impairment in V_T expansion due to the constant pressure throughout inspirations and premature termination of inspirations which has previously been observed in well trained-rowers during high intensities of pressure-threshold loading (McConnell & Griffiths, 2010). In the present study, the application of TFRL allowed V_T, and consequently $\dot{V}_E$, to reach levels threefold of those observed by de Souza et al. (2016). The greater expansion of V_T during TFRL therefore allows for greater external work to be performed per breath, and allows participants to tolerate higher training loads compared to when using pressure-threshold loading (Langer et al., 2015).

5.4.3. Gas exchange responses

End-tidal CO_2 decreased significantly from baseline levels at all inspiratory loaded intensities in both age groups. Previous literature has reported a fall in end-tidal CO_2 of 16.2 mmHg from baseline over two bouts of 30 inspiratory muscle loaded breaths at 40 % PI_{max} (Ross et al., 2007). The participants in this study were instructed by Ross et al. (2007) to perform each loaded inspiration near RV and terminate toward TLC with no further instructions given relating to breathing pattern. Due to the increase in V_T during inspiratory muscle loading, the authors noted a decreased breathing frequency from resting values and explained this as an advantageous pattern adopted to offset the effects of hypocapnia (Ross et al., 2007). In the present study, breathing frequency was controlled, however, no specific instructions relating to V_T were given during the 10 breaths/min protocol. The fall of ∼7–9 mmHg in end-tidal CO_2 during inspiratory loading observed in the present study compared to 16.2 mmHg in the work of Ross et al. (2007) is likely due to a much shorter duration of loading (10 breaths compared to 2 × 30 breaths) and a lower $\dot{V}_E$ (∼25–30 L/min compared to 43.1 L/min).

Nevertheless, this study shows that even a short bout of inspiratory muscle loading at 10 breaths/min can result in significant reductions in end-tidal CO_2 regardless of intensity.

5.4.4. Comparisons of TFRL protocols

When participants were instructed to maximise their V_T during TFRL at 6 breaths/min, no significant difference in V_{EI} or V_{EE} between loaded trials were observed in either age group. This is in contrast to significantly lower total V_{EI} at 70% PI_{max} compared to 30% PI_{max} during TFRL at 10 breaths/min within the older group. This is likely due to the significantly lower V_{EE} at 70% PI_{max} during the 6 breaths/min compared to at 10 breaths/min, allowing the diaphragm to produce a greater pressure to overcome higher inspiratory resistances due to lengthened diaphragmatic fibres as outlined above (Kikuchi et al., 1991; Martin et al., 1982), and therefore resulted in a less restricted V_{EI} at higher inspiratory loads.

$P_{ET}CO_2$ values were significantly greater, and $P_{ET}O_2$ values significantly lower, during TFRL at 6 breaths/min compared to during TFRL at 10 breaths/min. These findings show that the reduced breathing frequency protocol allowed participants to avoid hyperventilation and offset the effects of hypocapnia even with maximum V_T breaths (Romer & McConnell, 2003; Ross et al., 2007).

Respiratory effort scores were significantly reduced at higher intensities of TFRL during the 6 breaths/min protocol compared to the 10 breaths/min protocol (at 70% only in younger adults, and 50% and 70% in older adults). An explanation for this may be that, although PI_{max} manoeuvres were performed from RV, no instructions were provided to allow participants to initiate their breaths from RV during the TFRL protocol at 10 breaths/min. Participants, therefore, initiated each loaded inspiration from FRC where, due to the length-tension relationship of the respiratory system and/or additional elastic recoil of the lung and chest wall, PI_{max} could be lower than when measured at RV (Windisch, Hennings, Sorichter, Hamm, & Criee, 2004). This implies that the intensities applied relative to PI_{max} during this protocol could be higher than reported and may explain the increased effort at higher intensities. During TFRL at 6 breaths/min where participants were specifically instructed to exhale to RV, as observed in previous studies (Langer et al., 2015; Van Hollebeke et al., 2020), the intensities applied relative to PI_{max} will have been identical and, along with the reduced hypocapnia, may explain the lower respiratory effort ratings during this protocol.

5.4.5. Limitations

Surface electromyography (sEMG) measurements of both inspiratory (external intercostals and sternocleidomastoid) and expiratory (rectus abdominus) muscle were unavailable as measurements of respiratory muscle activation. Furthermore, a respiratory muscle metaboreflex response has previously been observed during pressure-threshold loading at 60% PI_{max} (McConnell & Griffiths, 2010), however, due to the absence of heart rate and MAP in the present study meant that evidence of a respiratory muscle metaboreflex response during various intensities of TFRL could not be identified.

5.5. Conclusion

The findings from this chapter suggest that during short bouts of TFRL at high intensities, older adults have a significantly lower V_T expansion, occurring due to lower V_{EI}, and higher V_{EE} RC volumes. This is likely due to reduced elastic recoil of the lung and reduced compliance of the chest wall during the healthy ageing process. When inspirations were initiated from RV and breathing frequency was reduced to 6 breaths/min, participants had significantly higher $P_{ET}CO_2$ levels (reflecting less hypocapnia), significantly lower reported respiratory effort ratings, with no change in operational thoracoabdominal volumes being observed between intensities of TFRL. Combined, these findings suggest that participants were better able at tolerating the higher intensities (50% and 70% PI_{max}), highlighting the importance of this training protocol during TFRL.

This chapter utilised OEP measurements in healthy younger and older adults to investigate the effects of age on thoracoabdominal volume regulation during acute inspiratory muscle loading (via TFRL) at low, moderate, and high intensities. The findings that inspiratory muscle loading resulted in increases in compartmental thoracoabdominal volumes in older adults from this chapter provided a rationale for the subsequent chapter to further utilise OEP to investigate whether an 8-week IMT programme will result in changes in thoracoabdominal volume regulation during exercise in healthy older adults.

CHAPTER 6 – THE EFFECTS OF INSPIRATORY MUSCLE TRAINING ON THORACOABDOMINAL VOLUME REGULATION IN OLDER ADULTS

6.1. Introduction

This chapter investigated the effects of IMT on respiratory muscle function, exercise tolerance and thoracoabdominal volume regulation in healthy older adults. In chapter 3, a non-significant but clinically meaningful improvement in exercise capacity following IMT in healthy older adults was reported within the meta-analysis. The high heterogeneity from said meta-analysis highlighted the need for further studies with standardised procedures to fully determine the effects of IMT on exercise capacity within this population.

Previous studies in COPD patients have reported improvements in exercise capacity but with inconsistent findings relating to changes in breathing pattern during exercise following an IMT intervention. Some studies have observed significant increases in V_T (Charususin et al., 2016; Koppers et al., 2006; Wanke et al., 1994) and reductions in breathing frequency (bf; Charususin et al., 2016; Koppers et al., 2006; Petrovic et al., 2012), whilst others have reported improved exercise capacity with no significant changes in breathing pattern between groups (Langer et al., 2018). Charususin et al. (2016) concluded that they were unable to determine whether the observed increase in V_T was due to reduced mechanical restriction of V_T expansion (i.e., increased V_{EI}) or a reduction in dynamic hyperinflation (i.e. reduced V_{EE}). Furthermore, the available studies that have investigated the effect of IMT on operational lung volumes (Langer et al., 2018; Romer et al., 2002a; Turner, Mickleborough, McConnell, Stager, & Tecklenburg-Lung, 2011) did not utilise specific measurement techniques to separate operational volumes into compartments of the chest wall.

The measurement of total and compartmental thoracoabdominal volume regulation via OEP provides a solution to the aforementioned limitations. As evidenced in chapter 5, increases in total V_T during acute TFRL in older adults were due to comparable RC and AB V_T expansion, a finding also observed during pressure-threshold loading at 40% PI_{max} in this population (de Souza et al., 2016). Furthermore, moderate inspiratory muscle loading (both via TFRL within chapter 5 of the present thesis, and pressure-threshold loading within de Souza et al. (2016))

resulted in significantly increased RCa contribution compared to resting levels in older adults, reflecting greater work of the diaphragm during inspiration. It remains unclear whether repeated bouts of inspiratory muscle loading (in the form of IMT) will translate into enduring changes in total and compartmental thoracoabdominal volume regulation at rest and during exercise. To date, only two studies (Hoffman et al., 2021; Medeiros et al., 2019) have aimed to answer this question. Medeiros et al. (2019) observed a significant increase of 0.1 L in the RCp volume of chronic kidney disease patients during IC manoeuvres at rest following IMT compared to the control group. No difference, however, was observed during QB between groups. Hoffman et al. (2021) also reported no significant changes in breathing pattern or thoracoabdominal volume regulation, despite improvements in respiratory muscle strength and endurance in advanced lung disease patients. The authors stated that the main limitation of their study was the lack of OEP measurements during exercise and suggested that IMT may only elicit changes in breathing pattern when the respiratory system is placed under higher demands during exercise.

The systematic review and meta-analysis within chapter 3 of this thesis informed the study design of the current chapter, whereby a frequently used IMT protocol identified from previous literature (30 breaths, twice daily, at 50% PI_{max}) was implemented in an attempt to standardise methods between this study and existing studies (Ferraro et al., 2019; Mills et al., 2015; Rodrigues et al., 2021a, 2021b; Rodrigues et al., 2020; Rodrigues et al., 2018). Likewise, the 6MWT was chosen as a measure of functional capacity within this chapter to compare with previously reported findings following IMT in older adults (Huang et al., 2011; Mills et al., 2015; Rodrigues et al., 2018).

The aim of this study was threefold: 1) to determine whether IMT improves respiratory muscle strength, breathing discomfort, and exercise tolerance in healthy older adults, 2) to investigate whether changes in thoracoabdominal volume regulation are observed during exercise following IMT, and 3) to investigate whether IMT improves secondary outcomes such as physical activity levels, balance, and quality of life. It was hypothesised that IMT would result in significant improvements in inspiratory muscle strength (PI_{max}) and reduce sensations of breathing discomfort at a given fraction of PI_{max} compared to the control group. In turn, the aforementioned IMT-induced physiological changes were expected to translate into improved exercise capacity (6MWD) and/or increased relative contribution of the RC compartments to V_T expansion during exercise.

6.2. Methods

6.2.1. Study design

This was a randomised controlled study investigating the effects of IMT on exercise capacity and thoracoabdominal volume regulation during exercise compared to SHAM-IMT. Following the baseline assessment, participants were randomly allocated to either the experimental (IMT) or control (SHAM-IMT) group using an online randomisation programme (www.sealedenvelope.com). Stratification was based on the median percentage predicted PI_{max} observed for the older group within chapter 5 (<88% PI_{max} or ≥88% PI_{max}). This study was approved by Northumbria University Newcastle Ethics Committee (No: 23701).

6.2.2. Participants

Twenty-four older adults were initially recruited for this study. Inclusion and exclusion criteria outlined in chapter 4 were followed. All participants provided full informed consent (Appendix 4) before being randomised into experimental (IMT) or control (SHAM-IMT) groups.

Estimation of sample size was based on results published by Watsford and Murphy (2008). The mean difference in PI_{max} following training between the experimental and control group (17 cmH2O), and a standard deviation (SD) of 15 cmH2O was used with an alpha significance level of 0.05 (2-sided) and 80% power. A minimum total sample size was calculated to be 12 participants in each group to detect significant differences in PI_{max} between experimental and control groups.

6.2.3. Pre- and post-intervention outcome measures

Participants visited the lab on three separate occasions. Visit one included baseline assessments (outlined within chapter 4) of stature, mass, spirometry, pulmonary and respiratory muscle function, and breathing discomfort at a given level of inspiratory muscle strength. Blood pressure, exercise capacity (6MWT and CWR cycling), balance (mini-BEST), and quality of life (SF-36) were also assessed (specific details of these procedures are described within the following sections). Participants were then randomised into groups outlined above and trained for 8-weeks following a specific protocol (outlined within the *"interventions"* section below). Visit two occurred at the mid-point of the 8-week intervention and involved reassessments of maximal respiratory pressures to ensure those in the experimental group were still training at the predetermined intensity. Visit three occurred immediately after the 8-week IMT programme and involved post-intervention assessments of all outcomes assessed in visit 1. Physical activity levels were assessed in the week before visit 1 and the week immediately following visit 3.

6.2.3.1. Pulmonary and respiratory muscle function measurements

Pulmonary and respiratory muscle function was assessed as described in chapter 4 at baseline, mid-intervention, and post-intervention. Furthermore, breathing discomfort at a given fraction of PI_{max} was assessed during all 3 visits via the 10-point modified Borg scale following a bout of IMT (30 breaths at 50% baseline PI_{max}).

6.2.3.2. Six-minute walk test (6MWT)

The 6MWT is a self-paced measure of exercise capacity and involved participants walking as far as possible along a 30-metre flat course in accordance with ATS/ERS guidelines (Holland et al., 2014). Participants were instructed to walk as far as possible in 30 m shuttles at their own pace for six minutes. The 6MWD was recorded by tallying the number of 30 m laps covered by the participants as well as the number of meters achieved in the final partial lap (Holland et al., 2014).

6.2.3.3. Constant work rate (CWR) exercise test

CWR exercise tests were performed on a cycle ergometer. Predicted work rate max levels of each participant were calculated using equations from Lewthwaite et al. (2020). These equations were validated by the authors who found that the predicted values were statistically equivalent to values measured at peak cardiopulmonary exercise testing (Lewthwaite et al., 2020).

Following a warm-up of 3 minutes unloaded pedalling, participants performed the CWR test at 75% predicted work rate peak with a pedalling frequency of 60 rpm to their perceived limit of tolerance. IC manoeuvres were performed at rest, and every two minutes during the CWR test as previously described (O'Donnell & Webb, 1993) to establish thoracoabdominal volumes at TLC. Operational thoracoabdominal volumes and central haemodynamic responses were measured continuously via OEP (outlined in chapter 4) and bio-impedance cardiography (outlined below), respectively. Perceived dyspnoea and leg discomfort were assessed via the modified 10-point Borg scale (outlined in chapter 4), and oxygen saturation (SpO_2) was assessed via pulse oximetry, at rest, and every two minutes of exercise (outlined below). The exact same absolute load and protocol was used following the intervention.

6.2.3.4. Physical activity levels

Physical activity levels were measured via accelerometery (Actigraph wGT3X; ActiGraph, Pensacola, FL, USA) during the week preceding, and the week following completion of, the IMT intervention. Specifically, the outcome measures recorded by the ActiGraph were daily steps, vector magnitude count (VMC), sedentary, light, and MVPA levels.

The initialisation of the Actigraph was set to record for seven days (starting the day after the administration to the participant). The Actigraph was deployed in delay mode during day 0 and commenced logging at 07:00 hrs with a 7-day stop time indicated. The data collection sample rate was set to 100 Hz and an epoch length of 60 seconds. Participants were instructed to wear the ActiGraph around their waist during all hours of wakefulness. During data processing, a valid recording was defined as at least 8 hours (480 minutes) of wear time during waking hours (Demeyer et al., 2014). A minimum of 4 valid days (preferably weekdays) were required to be included within the data analysis (Demeyer et al., 2021).

6.2.3.5. Balance tests

Balance was chosen as a secondary outcome measure within this study due to the respiratory muscles, including the diaphragm (Hodges & Gandevia, 2000a, 2000b), and intercostal muscles (Hudson, Butler, Gandevia, & De Troyer, 2010) playing a role in postural stability. Furthermore, recent work has observed evidence of IMT improving postural stability in older adults which may result in the prevention of falls in this population (Ferraro et al., 2019).

A range of balance measures were assessed using the mini-balance evaluation systems test (mini-BEST), developed by Franchignoni, Horak, Godi, Nardone, and Giordano (2010), at baseline and post-intervention. This test is comprised of 14 tasks divided into four domains: anticipatory postural adjustments, reactive postural responses, sensory orientation, and dynamic balance during gait (Franchignoni et al., 2010). The mini-BEST test was developed from the original BESTest (Horak, Wrisley, & Frank, 2009) via psychometric (Factor and Rasch) analysis to significantly reduce the time taken to administer from 30–45 minutes to 10–15 minutes (Franchignoni et al., 2010; Potter & Brandfass, 2015). Each task within the mini-BEST is scored on a 3-point ordinal scale (0 = severely impaired, 1 = moderately impaired, and 2 = normal) with a maximum scorer of 28 points and a cut-off score of 16 to define older adults with balance disorders (Yingyongyudha, Saengsirisuwan, Panichaporn, & Boonsinsukh, 2016).

The mini-BEST has been shown to have high test-retest (intraclass correlation coefficient; ICC = 0.96) and interrater (ICC = 0.98) reliability in older adults with mixed diagnoses (Godi et al., 2013). These findings for good to excellent reliability (ICC >0.90) are consistent across populations including stroke (Tsang, Liao, Chung, & Pang, 2013) and Parkinson's disease (Leddy, Crowner, & Earhart, 2011). Furthermore, the mini-BEST has been shown to have high validity in measuring baseline balance and its change over time (Franchignoni et al., 2010; Godi et al., 2013). A MCID value, representing the smallest change in score which likely reflects true change rather than measurement error alone, was suggested to be 4-points for the mini-BEST (Godi et al., 2013).

6.2.3.6. Quality of life

Quality of life (QoL) was assessed via the SF-36 (Ware Jr & Sherbourne, 1992). This questionnaire consists of 36 questions across eight dimensions of health: physical function, role physical, bodily pain, general health perception, vitality, social function, role emotional, and mental health. Scores for each dimension were coded, summed, and transformed onto a scale ranging from 0 (worst health) to 100 (best health) as outlined previously (Brazier et al., 1992).

6.2.3.7. Central haemodynamic measurements

Central haemodynamic variables including cardiac output, stroke volume, and heart rate were recorded continuously, and averaged at 6-second intervals, at rest, during CWR exercise and recovery via a non-invasive bioimpedance cardiography device (PhysioFlow, Enduro, PF-07, Manatec Biomedical, France).

Following skin preparation, six electrodes were attached to the participant: two on the left carotid (Z1 and Z2), two on the chest (ECG1 and ECG2; corresponding to positions V1 and V6 used for conventional electrocardiogram [ECG] monitoring), and two on the back in line with the xiphisternum (Z3 and Z4/ECG3/neutral; Figure 6-1) as outlined by Nasis et al. (2015) and Tan, Lai, and Hwang (2006). Participants were then required to sit in a relaxed position whilst the device calibrated on 30 consecutive heartbeats, with the best possible signal stability.

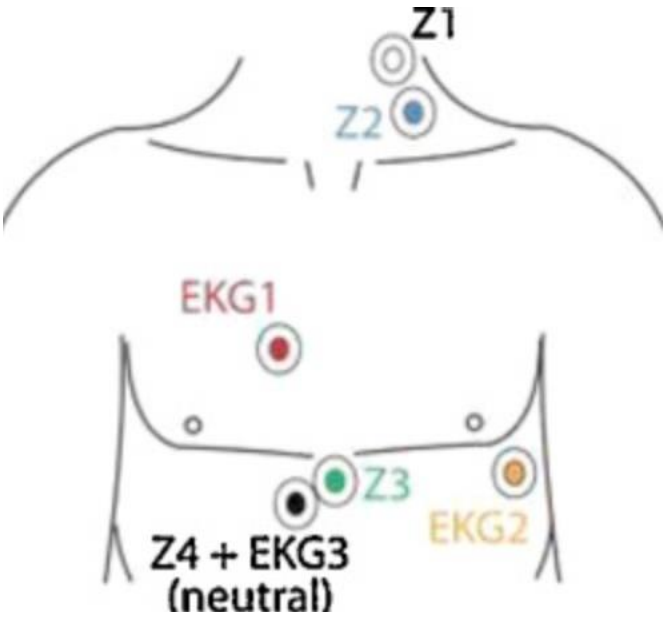


Figure 6-1. The recommended sites for the six PhysioFlow electrode placement (Nasis et al., 2015).

This technique of non-invasively recording beat-by-beat changes in cardiac output via cardio-impedance provides an automated and continuous measurement (Charloux et al., 2000) and uses equations to calculate stroke volume originally proposed by Kubicek, Karnegis, Patterson, Witsoe, and Mattson (1966) and modified by Bernstein (1986). The PhysioFlow measures changes in transthoracic impedance (d*Z*) in response to a high-frequency (75 kHz) emissions and low-intensity (3.8 mA peak to peak) alternating electrical current during cardiac ejection (Tonelli, Alnuaimat, Li, Carrie, & Mubarak, 2011). This device is therefore able to establish stroke volume index (SVi) independent of baseline impedance (Z_O) by relying on change in dZ, thus allowing the avoidance of variations due to skin thickness, hydration status, electrode positioning, and blood resistivity (Tan et al., 2006; Tonelli et al., 2011).

Stroke volume measured by cardio-impedance (SV_{PF}) is based on the following formula outlined by Bougault et al. (2005):

$$CO_{PF} = HR_{PF}\ x\ SVi\ x\ BSA$$

where CO_{PF} is cardiac output (litres/min) measured by cardio-impedance, HR_{PF} is heart rate (beats/min) based on the R-R interval determined by the ECG derivative, SVi is stroke volume index (ml/m^2 of BSA; SVi = SV/BSA), and BSA is body surface area (m^2) according to the formula below:

$$BSA = 0.024265\ x\ BM^{0.5378}\ x\ H^{0.3964}$$

where BM is body mass (kg) and H is height (cm). During the calibration, the first SVi evaluation records the largest Z variation during ventricular systole (maximum Z – minimum Z) along with the largest Z signal variation (contractility index; dZ/dtMAX). Furthermore, the PhysioFlow device also uses the thoracic flow inversion time (TFIT), which reflects the time interval between the first zero value following the beginning of the cardiac cycle and the first nadir after peak ejection velocity (dZ/dtMAX; Figure 6-2). TFIT is weighted using specific algorithm taking into account heart rate and arterial tension difference (systolic arterial tension – diastolic arterial tension). The formula for SVi at calibration (SVi_{CAL}) is outlined below:

$$SV_{CAL} = k\ x\ [(dZ/dtMAX)/maximumZ - minimumZ)]\ x\ weightedTFIT_{CAL}$$

where k is a constant.

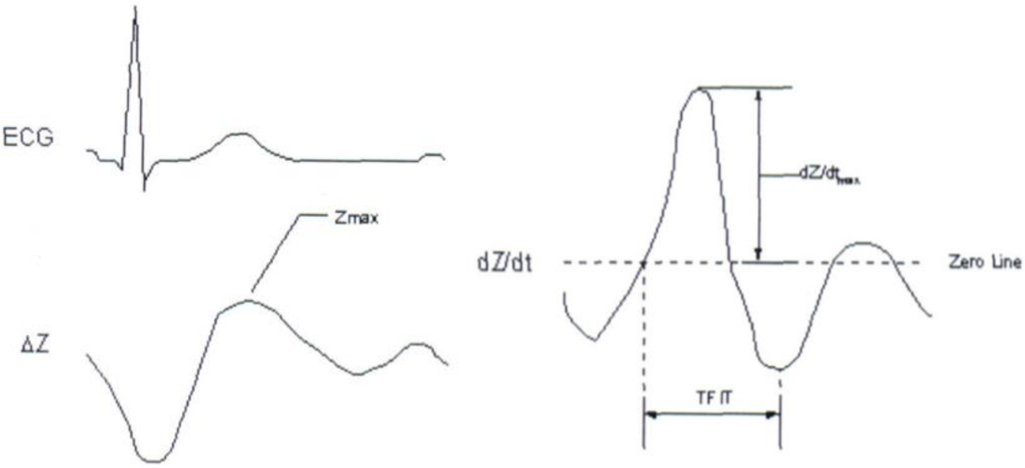


Figure 6-2. PhysioFlow waveforms obtained from Bougault et al. (2005). ΔZ, bioimpedance signal; Zmax, maximum bioimpedance signal; dZ/dt, contractility index; dZ/dtMAX, peak ejection velocity; TFIT, thoracic flow inversion time.

Overall, the PhysioFlow uses bioimpedance to calculate stroke volume using the following equation:

$$SV = BSA\ x\ SViCAL\ x\ \sqrt[3]{[(dZ/\mathrm{dtMAX})/(\mathrm{dZ/dtMAX}\ at\ calibration)\ x\ TFIT\ at\ calibration\ /TFIT]}$$

A number of studies have investigated the accuracy and reliability of the PhysioFlow device in measuring cardiac output at rest and during submaximal and maximal exercise (Charloux et al., 2000; Louvaris et al., 2019; Tan et al., 2006). Charloux et al. (2000) compared measurements of cardiac output via impendance cardiography (PhysioFlow) to the direct Fick method an found that the PhysioFlow device can provide clinically acceptable evaluation of cardiac output at rest and during submaximal exercise in individuals with normal cardiorespiratory function, airway obstruction, and thoracic hyperinflation.

Studies, however, have shown a slight over-estimation of cardiac output values recorded by PhysioFlow when compared to invasive methods (Bougault et al., 2005; Kemps et al., 2008; Louvaris et al., 2019). In the study conducted by Louvaris et al. (2019), the researchers compared cardiac output measurements captured by the PhysioFlow and by the indocyanine green dye dilution methods in patients with COPD from rest to peak exercise. The authors found a strong correlation between methods (mean percentage difference: 18%) with the PhysioFlow yielding systematically higher values. When data was expressed as changes from rest, however, correlations and agreement between methods remained strong throughout the exercise range.

6.2.3.8. Oxygen saturation (SpO_2) measurements

Resting and exercise (CWR tests) measures of SpO_2 were taken via pulse oximetry (Nonin, Palm SAT 2500, USA) placed on a finger of preference. The accuracy of pulse oximetry taken from the finger has previously been reported within a meta-analysis conducted by Jensen, Onyskiw, and Prasad (1998) who observed an accuracy of between 2 and 5% of in vitro oximetry when SpO_2 values were between 70 and 100%. Furthermore, within the 21 included pulse oximeter models, the authors reported a correlation coefficient between 0.986 and 0.591 (Jensen et al., 1998).

6.2.4. Interventions

The training programme within this study consisted of two daily, home-based sessions of 30 breaths, 7 days/week for 8 weeks using a pressure-threshold IMT device (POWERbreathe Classic [medium resistance], POWERbreathe International Ltd., Southam, UK; Figure 6-3). The IMT group trained at an intensity corresponding to approximately 50% of their baseline PI_{max}, ensuring maximum inspirations were achieved during each breath, and aiming for Borg scale ratings of 4–6 for perceived breathing discomfort following each session. As this was mainly a home-based intervention, participants were coached through the correct technique prior to the intervention. This included inspiring forcefully against the resistance (lasting 1-2 seconds) followed by a slow expiration to RV (lasting around 4 seconds; McConnell, 2013). Participants were recommended to perform each training session in an upright seated position and if sensations of light-headedness occur, they should take a short pause of 2–3 seconds following exhalation.

Figure 6-3. The POWERbreathe Classic device which was used to perform inspiratory muscle training.

Training diaries were administered to monitor adherence to the intervention, and participants were instructed to record the intensity (level 1–9 on the POWERbreathe Classic device which was converted to % baseline PI_{max} during analysis), duration (number of breaths achieved; should always be around 30) and breathing discomfort (using a modified 10-point Borg scale provided) following each session (Appendices 6 and 7). Participants were encouraged to increase the training load by a one quarter turn of the load tensioner (2–3 cmH_2O) if they reached the 30 breaths with ease (Borg rating of perceived breathing discomfort <4). The control (SHAM-IMT) group trained as above but at an unaltered intensity of <15% PI_{max} (or lowest possible intensity on the device; 10 cmH_2O) for the entire 8 weeks.

After 4 weeks, all participants were required to return to the laboratory at Northumbria University for a mid-intervention visit to re-assess PI_{max} and adjust training load, if necessary, to ensure that those in the IMT group were training at approximately 50% of their current PI_{max}.

6.2.5. Statistical analysis

Normal distribution was assessed using the Shapiro-Wilk test, with a p value >0.05 indicating normally distributed data. Data are presented as mean ± SD unless stated otherwise. Baseline characteristics between groups were assessed via independent t-tests. Two-way repeated measures ANOVAs with Bonferroni adjustments were employed to determine within (pre-post/pre-mid-post [baseline, mid-, and post-intervention] and time [exercise isotime; 25, 50, 75, and 100%]) and between group (intervention [IMT vs. control]) interactions following training.

Isotime was defined as the duration of the shortest CWR test (pre- or post-intervention) for each individual and exercise isotime data are reported as a fraction of the shortest CWR test (i.e., 25, 50, 75, and 100%). Paired samples t-tests were employed to assess within group pre- vs post-intervention differences. Pearson's correlation analysis was performed in order to determine the association between changes from QB (delta Δ) in RC volume and changes from QB in total thoracoabdominal volume, as well as between changes from QB in AB volume and changes from QB in total thoracoabdominal volume during CWR exercise. T-tests were employed to determine between and within group differences in regression slopes. For all analyses, the level of significance was set to $p<0.05$.

6.3. Results

6.3.1. Participant baseline characteristics

Initially, 24 participants were recruited for this study, however, one participant within the IMT group dropped out due to illness. Demographic, spirometric, and respiratory muscle strength variables at baseline are outlined in Table 6-1. Other than a significant difference in age (p=0.048), no differences in baseline characteristics were observed between the IMT and control group. Adherence to the training sessions was 95.5 ± 6.5% and 92.2 ± 8.8% in the IMT and control groups, respectively, and were not significantly different (p=0.213). Weekly training intensity progression and breathing discomfort ratings in both the IMT and control groups are outlined in figure 6-4.

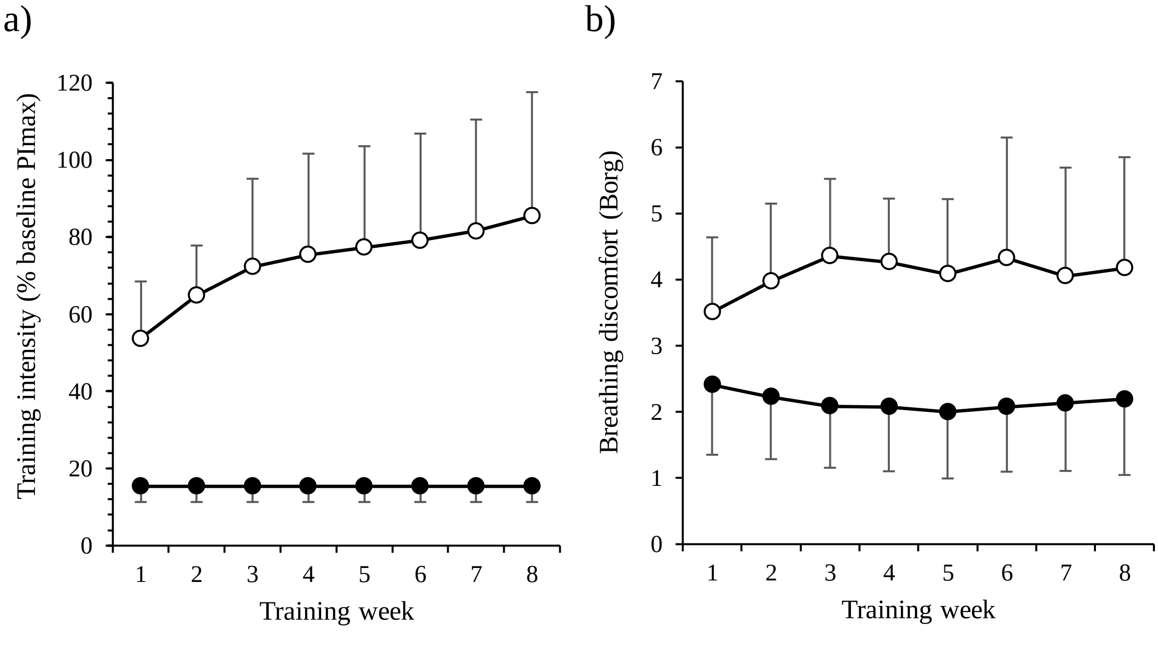


Figure 6-4. Average weekly training session intensity (expressed as percentage baseline PI_{max}; *a*) and breathing discomfort (expressed as Borg scale ratings; *b*) within the IMT (*open symbols*) and control group (*closed symbols*). Data presented as mean ± SD.

Table 6-1. Participant baseline characteristics.

	All participants (n=23)	IMT (n=11)	Control (n=12)
Men/Women (n)	11/12	5/6	6/6
Age (years)	68.3 ± 2.5	69.5 ± 2.3	67.3 ± 2.5*
Stature (cm)	168.9 ± 9.9	167.9 ± 8.2	169.8 ± 11.8
Mass (kg)	75.6 ± 17.2	79.8 ± 20.7	71.7 ± 13.9
BMI (kg/m^2)	26.3 ± 5.0	28.1 ± 5.8	25.1 ± 3.8
SBP (mmHg)	129.0 ± 15.1	132.0 ± 15.0	126.3 ± 16.0
DBP (mmHg)	81.1 ± 8.5	84.4 ± 7.8	78.2 ± 8.7
FEV$_1$ (L)	2.9 ± 0.8	2.7 ± 0.8	3.0 ± 0.9
FEV$_1$ (% predicted)	104.3 ± 14.8	102.5 ± 13.2	106.2 ± 16.6
FVC (L)	3.6 ± 1.0	3.5 ± 0.9	3.8 ± 1.1
FVC (% predicted)	102.3 ± 13.9	100.3 ± 12.9	104.3 ± 15.5
FEV$_1$/FVC (%)	78.6 ± 4.0	78.7 ± 4.7	78.4 ± 3.6
FEV$_1$/FVC (% predicted)	101.5 ± 6.1	101.7 ± 7.3	101.3 ± 5.2
PEF (L/s)	6.9 ± 2.3	6.9 ± 2.4	6.9 ± 2.5
PEF (% predicted)	98.9 ± 21.8	101.1 ± 24.1	96.7 ± 21.4
PI$_{max}$ at RV (cmH$_2$O)	80.5 ± 25.7	77.3 ± 26.5	83.4 ± 25.7
PI$_{max}$ at RV (% predicted)	94.1 ± 25.3	91.5 ± 25.9	96.4 ± 26.7
PI$_{max}$ at FRC (cmH$_2$O)	67.1 ± 22.6	65.5 ± 22.2	68.7 ± 23.7
PE$_{max}$ at TLC (cmH$_2$O)	120.6 ± 38.4	122.5 ± 42.9	118.7 ± 37.3

Data presented as mean±SD. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FEV$_1$, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow; PI$_{max}$, maximal inspiratory pressure; RV, residual volume; FRC, functional residual capacity; PE$_{max}$, maximal expiratory pressure; TLC, total lung capacity.

6.3.2. Pulmonary function

No significant improvements were observed in FVC, FEV_1, FEV_1/FVC, or PEF variables following IMT in the experimental group (Table 6-2). Significant decreases were found in absolute (p=0.001) and % predicted (p=0.002) values for FEV_1 within the control group with the two-way ANOVA showing these changes to be significantly different from those after IMT (absolute: p=0.013, F=7.303; % predicted: p=0.016, F=6.792).

6.3.3. Respiratory muscle function

No significant correlation was found within the IMT group between baseline PI_{max} and post-intervention change in PI_{max} expressed as absolute values (n=11, *r*=0.461, p=0.153; Figure 6-5a) and percentage predicted (n=11, *r*=0.472, p=0.136; Figure 6-5b).

Significant intervention x pre-mid-post interactions were observed for PI_{max} at RV (expressed as both absolute [p=0.001, F=10.923] and % predicted [p<0.001, F=12.351] values), PI_{max} at FRC (p=0.041, F=3.445) and breathing discomfort (p<0.001, F=11.017; Figure 6-6; Table 6-2). These interactions were attributable to significant increases in PI_{max} measures and decreases in breathing discomfort within the IMT group only from baseline to mid-intervention (PI_{max} at RV [cmH_2O; p=0.001; % pred; p<0.001]; PI_{max} at FRC, p=0.005; breathing discomfort, p<0.001), baseline to post-intervention (p<0.001 for all variables), and from mid- and post-intervention (PI_{max} at RV [cmH_2O; p=0.036; % pred; p=0.043]; PI_{max} at FRC, p=0.008). No significant change in breathing discomfort in the IMT group was observed between mid- and post-intervention (p=0.080). No significant intervention x pre-mid-post interaction was observed for PE_{max} (p=0.838, F=0.177). No changes between intervention time-points were observed for any variable within the control group.

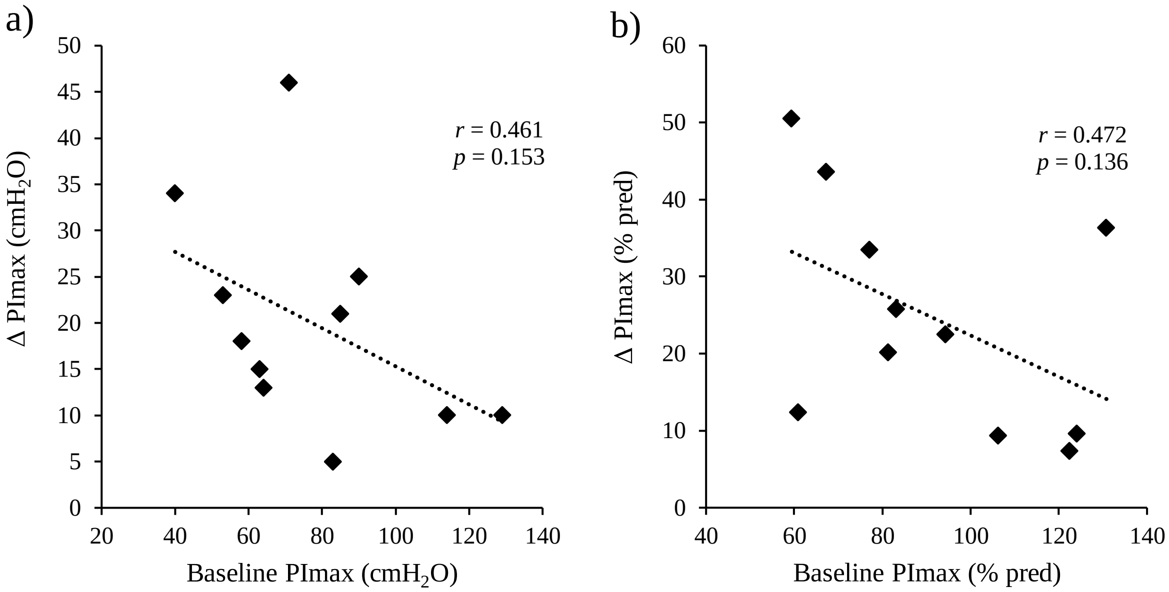


Figure 6-5. The association between baseline maximal inspiratory pressure (PI_{max}) and delta (Δ) PI_{max} within the IMT group expressed as absolute values (cmH_2O; a) and percentage predicted (% pred; b).

6.3.4. Blood pressure

Systolic blood pressure was significantly reduced following training in the control group only (p=0.039), however, no significant intervention x pre-post interaction was observed (p=0.819, F=0.054; Table 6-2). Diastolic blood pressure remained unchanged following training in both IMT (p=0.115) and control (p=0.096) groups.

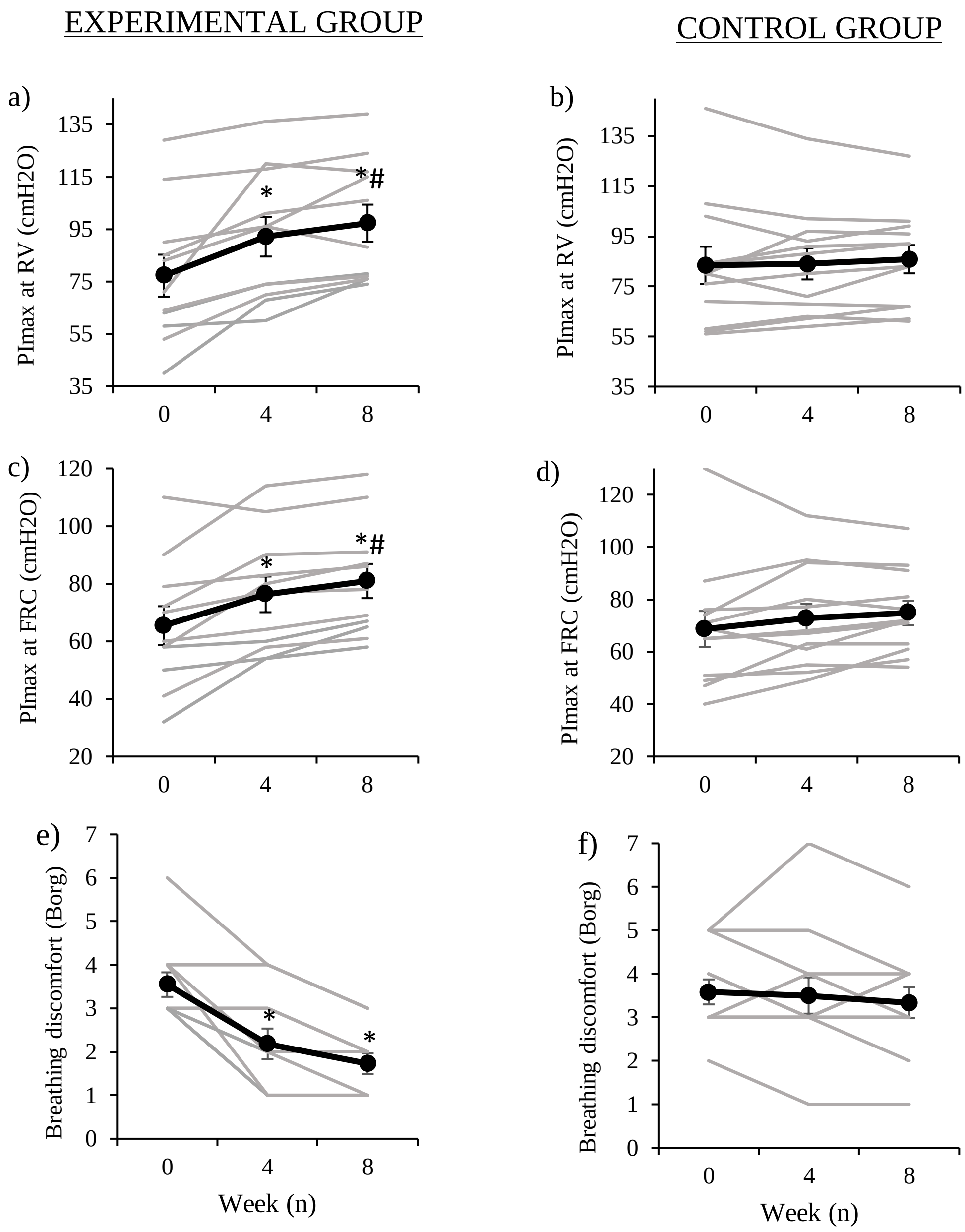


Figure 6-6. Individual changes in maximal inspiratory pressure (PI_{max}; measured at RV [*a and b*] and FRC [*c and d*]) and breathing discomfort (*e and f*) measured at baseline (0 weeks), mid-intervention (4-weeks), and post-intervention (8-weeks) for the IMT (left panels) and control groups (right panels). Thick lines represent mean±SEM. *denote significant difference from pre-intervention; $^{\#}$significant difference from mid-intervention.

Table 6-2. Baseline, mid- and post-intervention values for pulmonary function, blood pressure, respiratory muscle strength and breathing discomfort.

	IMT			**Control**		
	Baseline	Mid-intervention	Post-intervention	Baseline	Mid-intervention	Post-intervention
FEV$_1$ (L)	2.7 ± 0.8		2.7 ± 0.8	3.0 ± 0.9		2.9 ± 0.9*†
FEV$_1$ (% predicted)	102.5 ± 13.2		102.5 ± 11.5	106.2 ± 16.6		101.7 ± 15.5*†
FVC (L)	3.5 ± 0.9		3.5 ± 1.0	3.8 ± 1.1		3.7 ± 1.0
FVC (% predicted)	100.3 ± 12.9		101.7 ± 16.8	104.3 ± 15.5		101.3 ± 12.8
FEV$_1$/FVC (%)	78.7 ± 4.7		78.2 ± 6.0	78.4 ± 3.6		77.3 ± 4.8
FEV$_1$/FVC (% predicted)	101.7 ± 7.3		101.1 ± 7.9	101.3 ± 5.2		99.7 ± 6.9
PEF (L/s)	6.9 ± 2.4		6.7 ± 2.4	6.9 ± 2.5		6.9 ± 2.3
PEF (% predicted)	101.1 ± 24.1		98.1 ± 21.5	96.7 ± 21.4		95.8 ± 21.1
SBP (mmHg)	132.0 ± 15.0		127.0 ± 13.2	126.3 ± 16.0		122.3 ± 13.7*
DBP (mmHg)	84.4 ± 7.8		80.2 ± 6.0	78.2 ± 8.7		74.5 ± 10.0
PI$_{max}$ at RV (cmH$_2$O)	77.3 ± 26.5	92.1 ± 25.0*	97.3 ± 23.6*#	83.4 ± 25.7	84.0 ± 21.6	85.8 ± 19.5†
PI$_{max}$ at RV (% predicted)	91.5 ± 25.9	109.3 ± 21.9*	116.2 ± 23.0*#	96.4 ± 26.7	97.4 ± 23.0	99.5 ± 21.0†
PI$_{max}$ at FRC (cmH$_2$O)	65.5 ± 22.2	76.3 ± 20.6*	80.9 ± 19.8*#	68.7 ± 23.7	72.8 ± 19.4	74.8 ± 15.9†
PE$_{max}$ at TLC (cmH$_2$O)	122.5 ± 42.9	123.6 ± 54.7	130.7 ± 45.8	118.7 ± 37.3	118.4 ± 44.6	123.0 ± 41.6
Breathing discomfort (Borg scale)	3.5 ± 0.9	2.2 ± 1.2*	1.7 ± 0.8*	3.6 ± 1.0	3.5 ± 1.4	3.3 ± 1.2†

Data presented as mean±SD. SBP, systolic blood pressure; DBP, diastolic blood pressure; FEV$_1$, forced expiratory volume in one second; FVC, forced vital capacity; PEF, peak expiratory flow; PI$_{max}$, maximal inspiratory pressure; RV, residual volume; FRC, functional residual capacity; PE$_{max}$, maximal expiratory pressure; TLC, total lung capacity; Breathing discomfort rating based on the 1─10 Borg scale. *denote significant difference from pre-intervention; #significant difference from mid-intervention, †significant intervention x pre-post interaction.

6.3.5. Exercise capacity

No intervention x pre-post interaction was found for 6MWD (p=0.114, F=2.715) or CWR time (p=0.725, F=0.127), however, subsequent paired t-tests showed that 6MWD significantly increased in the IMT group (p=0.042) by 18.8 ± 28.4 m but did not change within the control group (p=0.956; Table 6-3). No significant intervention x pre-post x time interaction was observed for dyspnoea (p=0.440, F=0.913) or leg discomfort ratings (p=0.227, F=1.485). Paired t-tests revealed a significant decrease in dyspnoea ratings following training at 75% isotime within the control group only (p=0.005). Furthermore, leg discomfort ratings were significantly reduced following training in the IMT group at 50% (p=0.013) and 75% isotime (p=0.031).

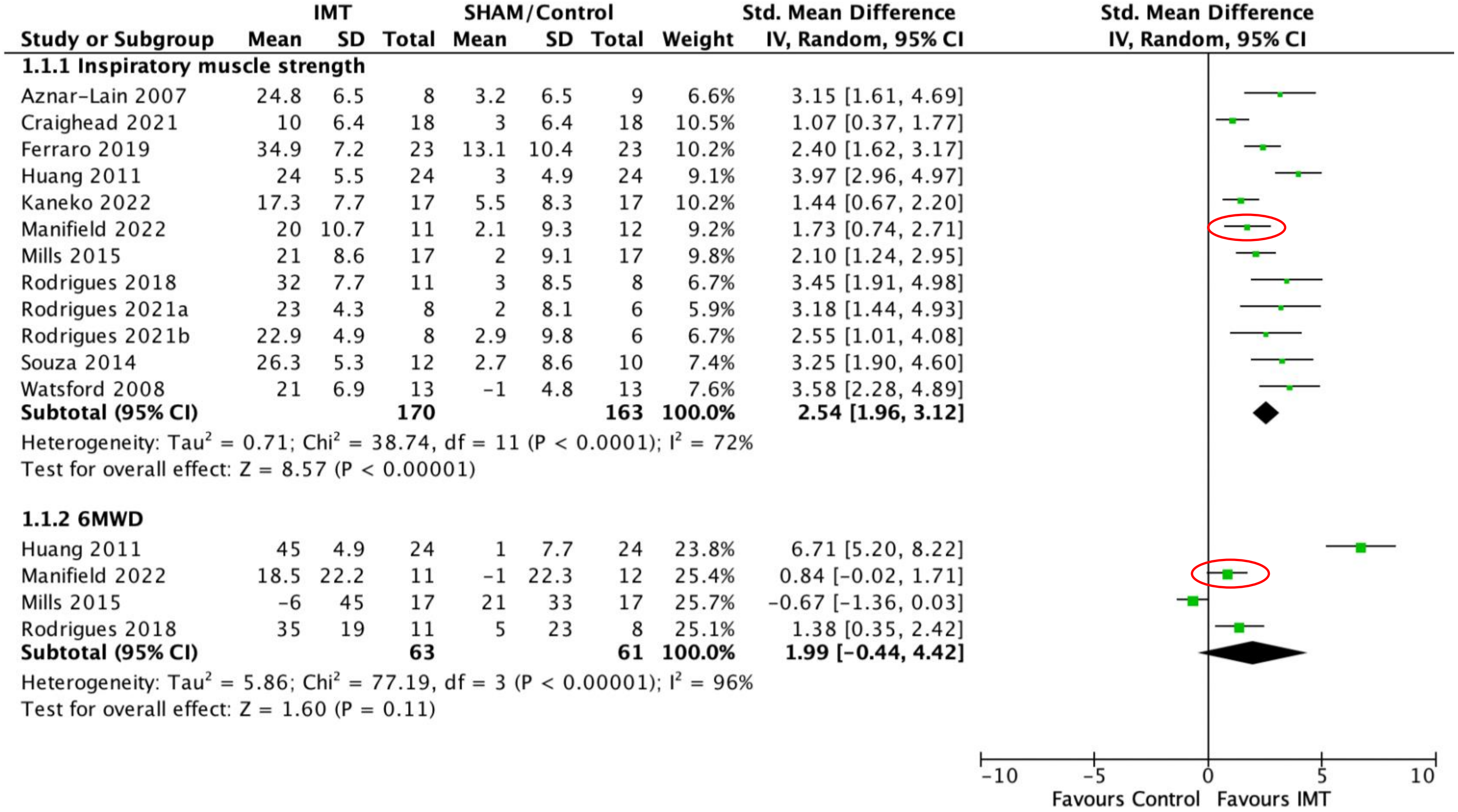
Table 6-3. Baseline and post-intervention values for exercise capacity.

	IMT		Control	
	Baseline	Post-intervention	Baseline	Post-intervention
6MWD (m)	588.7 ± 56.4	607.5 ± 48.0*	600.6 ± 54.0	600.1 ± 54.8
	CWR exercise			
Exercise time (s)	673.7 ± 415.2	676.8 ± 460.7	598.9 ± 276.1	577.7 ± 326.0
	Dyspnoea (Borg scale)			
25% isotime	1.8 ± 1.1	1.3 ± 1.1	1.8 ± 0.9	1.7 ± 1.0
50% isotime	3.2 ± 0.4	2.7 ± 1.0	3.1 ± 0.9	2.8 ± 0.8
75% isotime	4.3 ± 0.6	3.9 ± 0.8	4.3 ± 1.3	3.6 ± 1.1*
100% isotime	5.6 ± 1.6	5.1 ± 1.2	4.9 ± 1.7	4.4 ± 1.2
	Leg discomfort (Borg scale)			
25% isotime	2.5 ± 1.3	2.1 ± 1.2	2.5 ± 1.1	2.3 ± 1.1
50% isotime	3.8 ± 0.8	3.0 ± 1.3*	3.5 ± 0.9	3.3 ± 1.1
75% isotime	4.5 ± 0.9	4.2 ± 1.3	4.8 ± 1.6	4.4 ± 1.4
100% isotime	6.9 ± 1.8	5.8 ± 2.0*	6.0 ± 1.6	5.7 ± 1.3

Data presented as mean±SD. 6MWD, six-minute walk distance; *denote significant difference from pre-intervention; †significant intervention x pre-post interaction.

6.3.6. Updated meta-analyses from chapter 3

The addition of data reported within this chapter (Manifield, 2022) to the meta-analyses performed in chapter 3 (Figure 6-3) changed the effect size (standard mean difference with 95% confidence intervals) for inspiratory muscle strength from 2.63 (2.00, 3.26; $p<0.001$; Figure 3-2) to 2.54 (1.96, 3.12; $p<0.001$; Figure 6-7). For 6MWD, the addition of Manifield (2022), changed the effect size from 2.42 (−1.28, 6.12; $p=0.20$) to 1.99 (−0.44, 4.42; $p=0.11$).



Study or Subgroup	IMT Mean	IMT SD	IMT Total	SHAM/Control Mean	SHAM/Control SD	SHAM/Control Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Inspiratory muscle strength								
Aznar-Lain 2007	24.8	6.5	8	3.2	6.5	9	6.6%	3.15 [1.61, 4.69]
Craighead 2021	10	6.4	18	3	6.4	18	10.5%	1.07 [0.37, 1.77]
Ferraro 2019	34.9	7.2	23	13.1	10.4	23	10.2%	2.40 [1.62, 3.17]
Huang 2011	24	5.5	24	3	4.9	24	9.1%	3.97 [2.96, 4.97]
Kaneko 2022	17.3	7.7	17	5.5	8.3	17	10.2%	1.44 [0.67, 2.20]
Manifield 2022	20	10.7	11	2.1	9.3	12	9.2%	1.73 [0.74, 2.71]
Mills 2015	21	8.6	17	2	9.1	17	9.8%	2.10 [1.24, 2.95]
Rodrigues 2018	32	7.7	11	3	8.5	8	6.7%	3.45 [1.91, 4.98]
Rodrigues 2021a	23	4.3	8	2	8.1	6	5.9%	3.18 [1.44, 4.93]
Rodrigues 2021b	22.9	4.9	8	2.9	9.8	6	6.7%	2.55 [1.01, 4.08]
Souza 2014	26.3	5.3	12	2.7	8.6	10	7.4%	3.25 [1.90, 4.60]
Watsford 2008	21	6.9	13	-1	4.8	13	7.6%	3.58 [2.28, 4.89]
Subtotal (95% CI)			**170**			**163**	**100.0%**	**2.54 [1.96, 3.12]**
Heterogeneity: Tau^2 = 0.71; Chi^2 = 38.74, df = 11 (P < 0.0001); I^2 = 72%								
Test for overall effect: Z = 8.57 (P < 0.00001)								
1.1.2 6MWD								
Huang 2011	45	4.9	24	1	7.7	24	23.8%	6.71 [5.20, 8.22]
Manifield 2022	18.5	22.2	11	-1	22.3	12	25.4%	0.84 [-0.02, 1.71]
Mills 2015	-6	45	17	21	33	17	25.7%	-0.67 [-1.36, 0.03]
Rodrigues 2018	35	19	11	5	23	8	25.1%	1.38 [0.35, 2.42]
Subtotal (95% CI)			**63**			**61**	**100.0%**	**1.99 [-0.44, 4.42]**
Heterogeneity: Tau^2 = 5.86; Chi^2 = 77.19, df = 3 (P < 0.00001); I^2 = 96%								
Test for overall effect: Z = 1.60 (P = 0.11)								

Figure 6-7. Mean difference (95% CI) from baseline of the effect of inspiratory muscle training on inspiratory muscle strength (measured by maximal inspiratory pressure; n=12) and six-minute walk test distance (n=4) compared to control, including findings from chapter 6 of this thesis (Manifield 2022; *circled*).

6.3.7. Thoracoabdominal volume regulation and breathing pattern

Out of the included 23 participants, OEP data from two participants (one in each group) were not analysed due to technical difficulties. Pre- and post-training values for $\dot{V}_E$, breathing frequency (bf), and total V_T during QB and CWR exercise 'isotime' (25, 50, 75, and 100%) are shown below for the IMT (Figure 6-8) and control groups (Figure 6-9). No significant intervention x pre-post x time interactions were observed for $\dot{V}_E$ (p=0.371, F=1.067), bf (p=0.535, F=0.736), or total V_T when expressed as absolute (p=0.408, F=0.919) and %FVC (p=0.606, F=0.509).

A significant intervention x pre-post x time interaction was observed for inspiratory flow (p=0.038, F=2.992) and duty cycle (p=0.039, F=2.970) but not for expiratory flow (p=0.257, F=1.384), T_{TOT} (p=0.587, F=0.498), T_I (p=0.505, F=0.687), or T_E (p=0.305, F=1.237; Appendix 8). The significant interactions were predominantly due to significant differences between time points, with post-hoc Bonferroni tests revealing no significant differences between pre- and post-intervention measures in either group or between groups at any time point for inspiratory flow. A significant reduction in duty cycle was observed at 100% exercise isotime following training within the control group only (p=0.044), with the pre-intervention value being significantly lower in the IMT group compared to the control (p=0.017).

EXPERIMENTAL GROUP

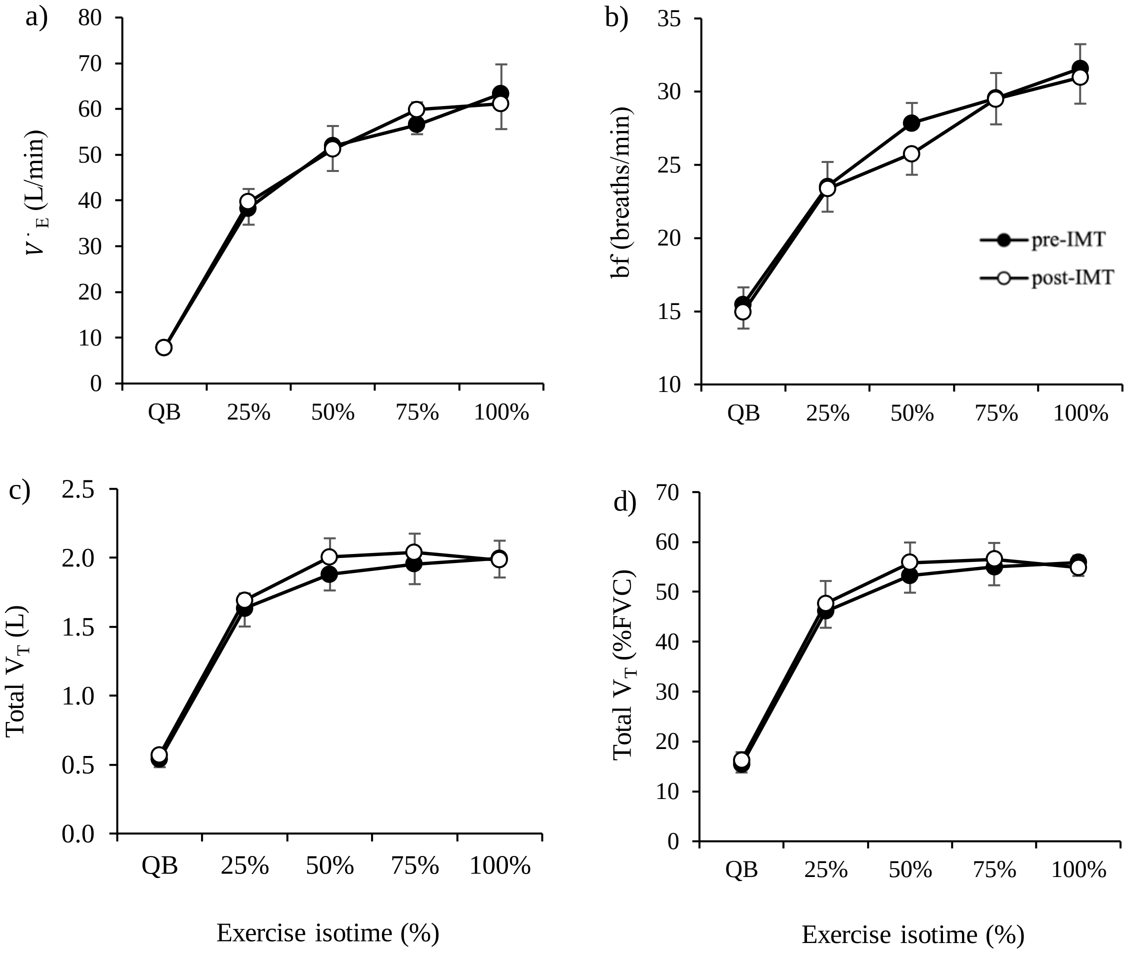


Figure 6-8. Minute ventilation ($\dot{V}_E$; a), breathing frequency (bf; b), and total tidal volume (V_T) expressed as absolute values (c) and %FVC (d) during constant work rate exercise before (closed symbols) and after (open symbols) IMT in the experimental group. Data presented as mean ± SEM.

CONTROL GROUP

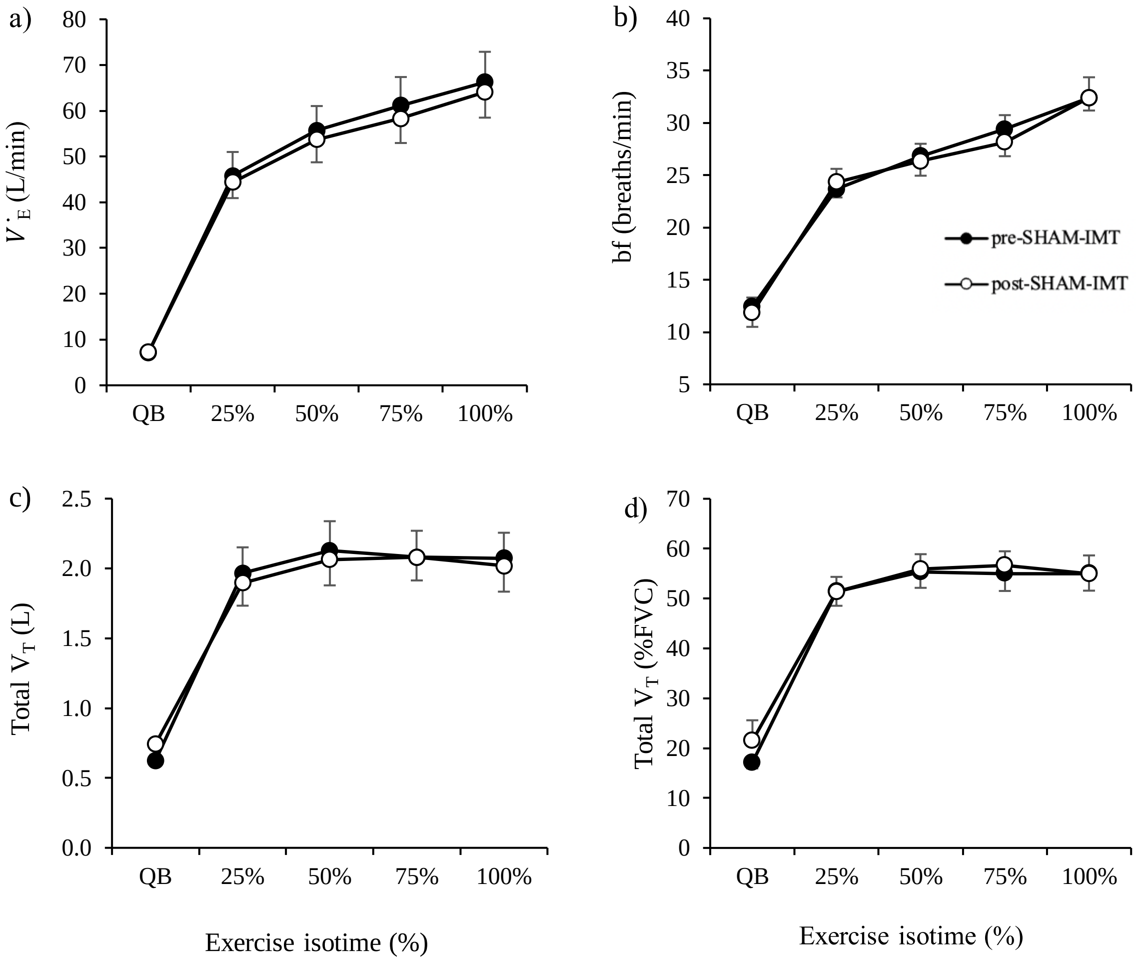


Figure 6-9. Minute ventilation ($\dot{V}_E$; a), breathing frequency (bf; b), and total tidal volume (V_T) expressed as absolute values (c) and %FVC (d) during constant work rate exercise before (closed symbols) and after (open symbols) SHAM-IMT in the control group. Data presented as mean ± SEM.

Compartmental (RCp, RCa, and AB) V_T during QB and CWR exercise 'isotime' (25%, 50%, 75%, and 100%) are shown below for the IMT (Figure 6-10) and control group (Figure 6-11). No significant intervention x pre-post x time interactions were observed for any compartmental V_T (RCp: p=0.316, F=1.184; RCa: p=0.847, F=0.159; AB: p=0.181, F=1.685). A significant intervention x pre-post interaction was found for RCa V_T only, with the IMT group showing higher values compared to control (p=0.028, F=5.630).

EXPERIMENTAL GROUP

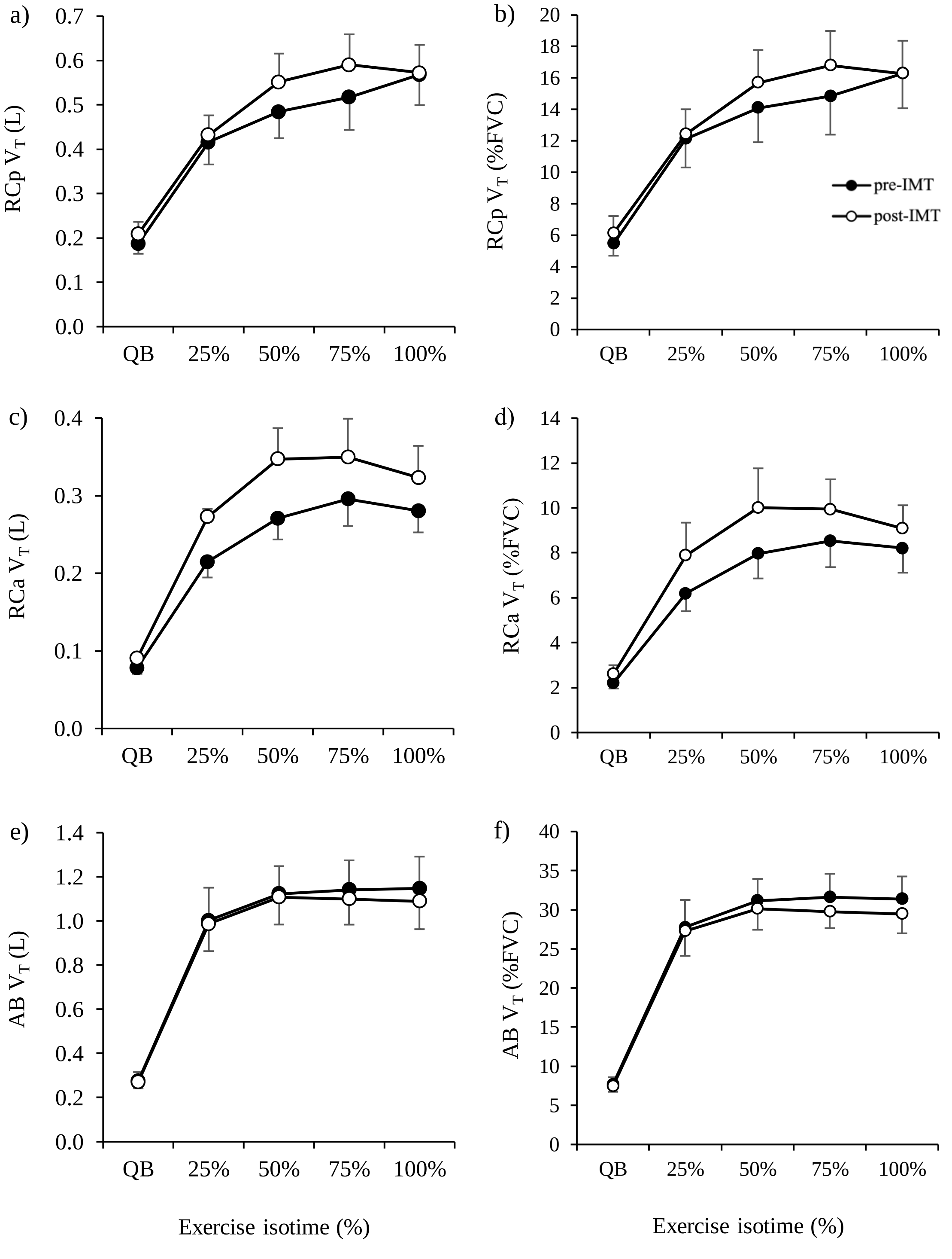


Figure 6-10. Compartmental (pulmonary rib cage [RCp], *a and b*; abdominal rib cage [RCa], *c and d*; and abdomen [AB], *e and f*) thoracoabdominal tidal volumes (V_T) expressed as absolute values (*right panels*) and %FVC (*left panels*) during constant work rate exercise before (closed symbols) and after (open symbols) IMT in the experimental group.

CONTROL GROUP

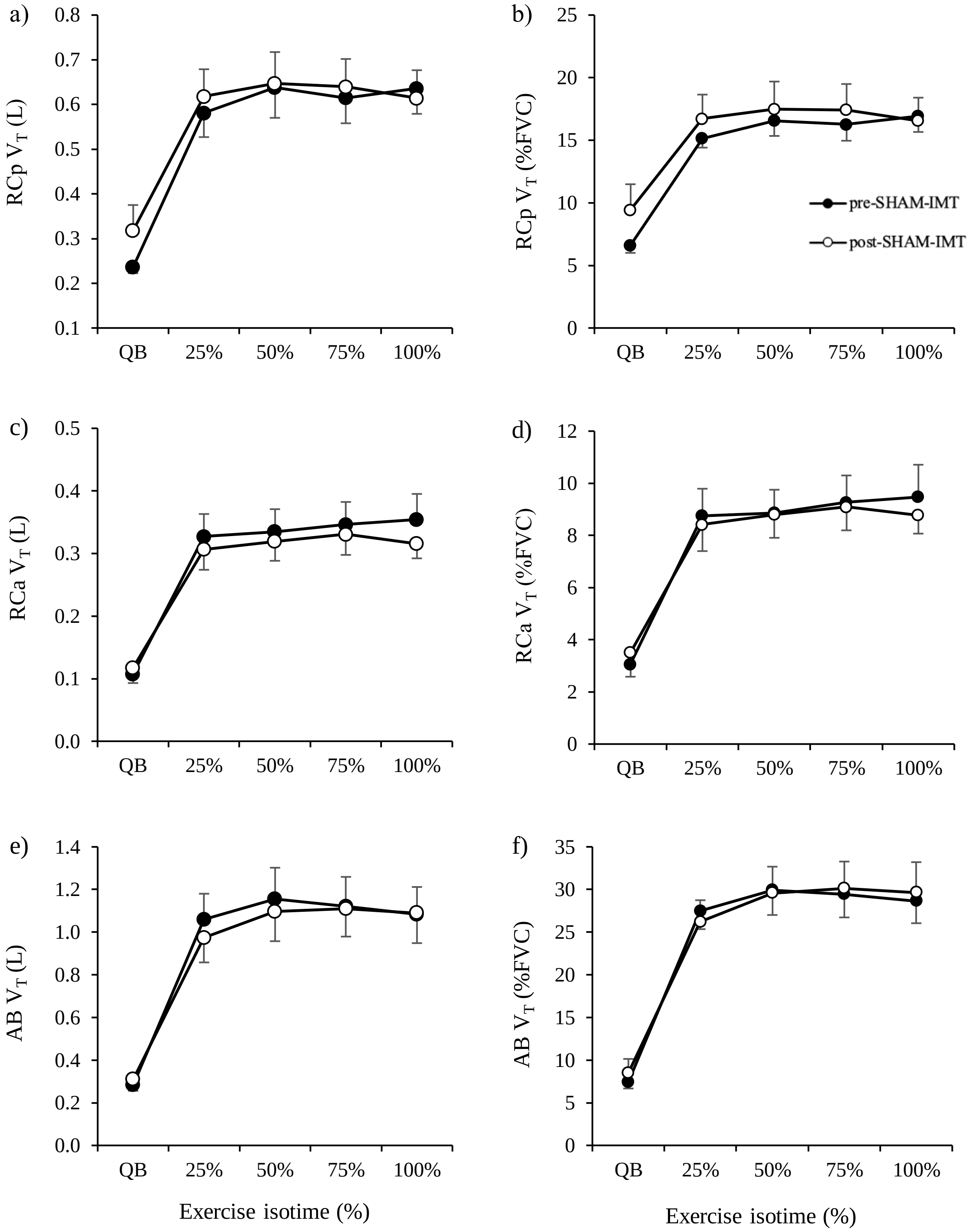


Figure 6-11. Compartmental (pulmonary rib cage [RCp], *a and b*; abdominal rib cage [RCa], *c and d*; and abdomen [AB], *e and f*) thoracoabdominal tidal volumes (V_T) expressed as absolute values (*right panels*) and %FVC (*left panels*) during constant work rate exercise before (closed symbols) and after (open symbols) SHAM-IMT in the control group.

V_{EI} and V_{EE} are shown during QB and CWR exercise 'isotime' (25, 50, 75, and 100%) for the IMT (Figure 6-12) and control groups (Figure 6-13). As with V_T responses, no significant intervention x pre-post x time interactions in end inspiratory (V_{EI}) volumes were observed within the total thoracoabdomen (p=0.123, F=2.008) or any of its compartments (RCp: p=0.401, F=0.929; RCa: p=0.410, F=0.978; AB: p=0.351, F=1.113). Furthermore, no significant intervention x pre-post x time interactions in V_{EE} were observed within the total thoracoabdomen (p=0.206, F=1.572) or any of its compartments (RCp: p=0.079, F=2.380; RCa: p=0.608, F=0.615; AB: p=0.497, F=0.805).

No significant intervention x pre-post interactions were observed for any of the aforementioned variables or total IC (p=0.487, F=0.503), however, the IMT compared to the control group exhibited greater post-intervention changes in $V_{RCa, EI}$ values, that fell short of statistical significance (p=0.059, F=4.042). No significant intervention x pre-post x time interactions were observed in total or compartmental values for V_{EI} or V_{EE} when expressed as %FVC (Appendix 9).

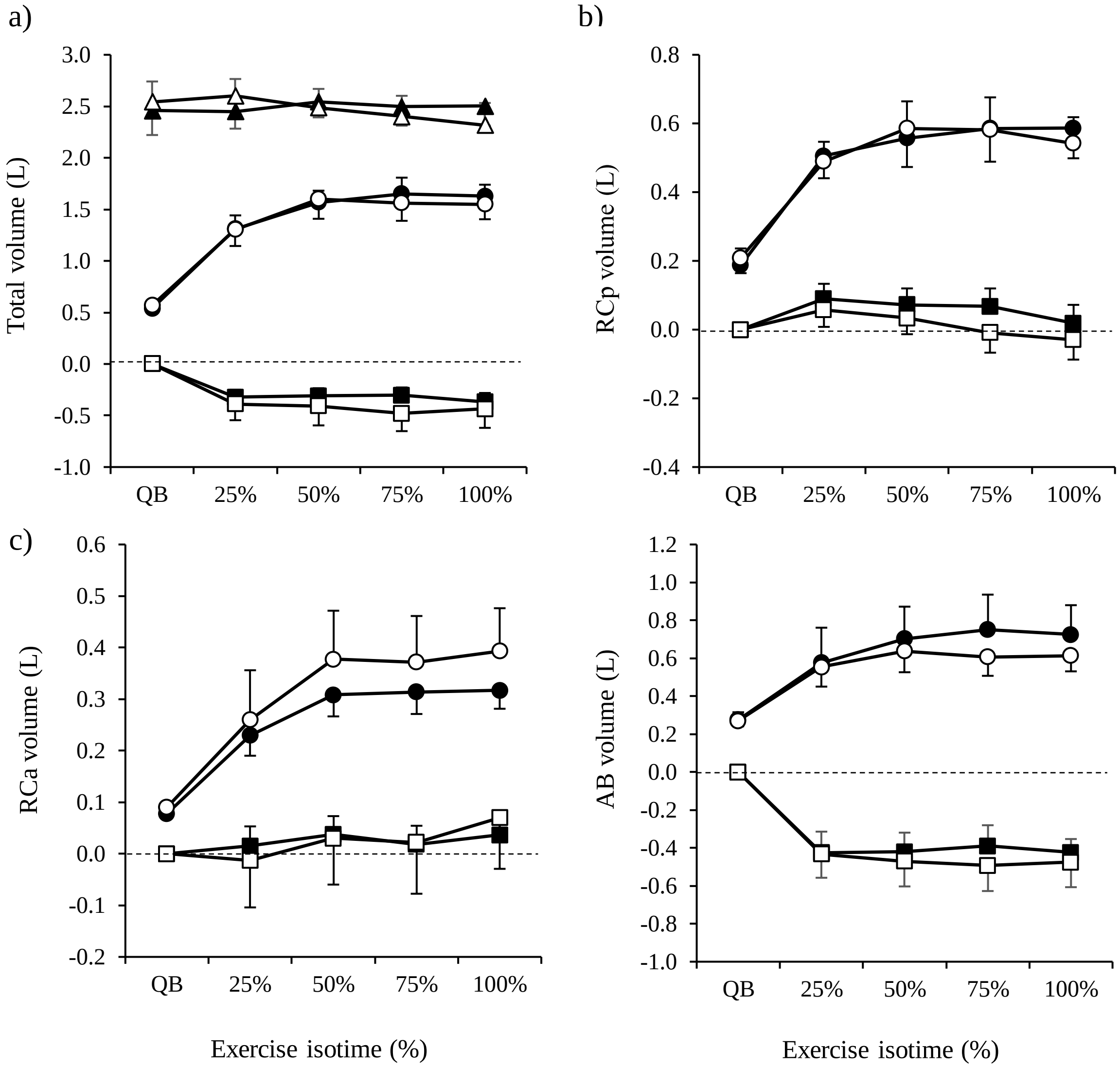


Figure 6-12. Volume (L) changes of the a) total thoracoabdomen, b) the pulmonary rib cage (RCp), c) the abdominal rib cage (RCa), and d) the abdomen (AB) within the IMT group at pre- (*closed symbols*) and post-intervention (*open symbols*) during quiet breathing (QB) and exercise isotime (25%, 50%, 75%, and 100%). *Circles* indicate end-inspiration, *squares* indicate end-expiration and *triangles* indicate chest wall volume at total lung capacity (TLC; $V_{CW,\ TLC}$). *Dashed line* indicates end-expiratory volume (V_{EE}) at quiet breathing (QB).

CONTROL GROUP

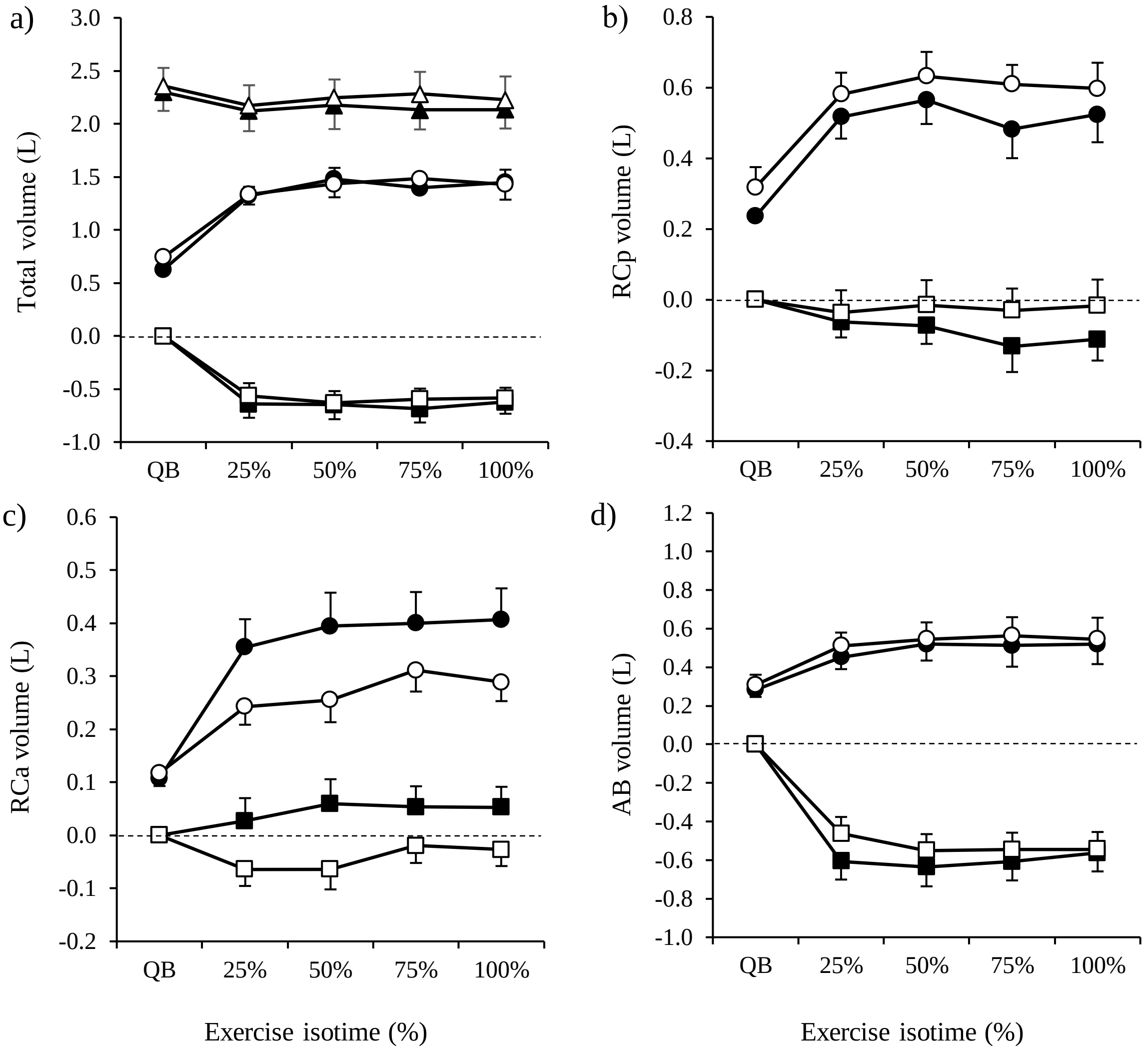


Figure 6-13. Volume (L) changes of the a) total thoracoabdomen, b) the pulmonary rib cage (RCp), c) the abdominal rib cage (RCa), and d) the abdomen (AB) within the control group at pre- (*closed symbols*) and post-intervention (*open symbols*) during quiet breathing (QB) and exercise isotime (25%, 50%, 75%, and 100%). *Circles* indicate end-inspiration, *squares* indicate end-expiration and *triangles* indicate chest wall volume at total lung capacity (TLC; $V_{CW,\ TLC}$). *Dashed line* indicates end-expiratory volume (V_{EE}) at quiet breathing (QB).

The association between changes (Δ) following training in rib cage (RC V_T) and total thoracoabdominal V_T, along with the association between changes in AB V_T and total thoracoabdominal V_T, during CWR exercise in both IMT and control groups are shown in Figure 6-14. A significant correlation between ΔRC V_T and Δtotal thoracoabdominal V_T was observed in the IMT group (r=0.781, p=0.008) but not in the control group (r=0.119, p=0.727). Furthermore, a significant correlation was observed between ΔAB V_T and Δtotal thoracoabdominal V_T in the control group (r=0.893, p<0.001) but not in the IMT group (r=0.134, p=0.713).

The regression slope for the association between ΔRC V_T and Δtotal thoracoabdominal V_T was significantly greater in the IMT group compared to the control group (p=0.012). Furthermore, the IMT group had a significantly lower regression slope for the association between ΔAB V_T and Δtotal thoracoabdominal V_T compared to the control group (p=0.012). In terms of within group differences, the regression slope for ΔRC V_T to Δtotal thoracoabdominal V_T compared to that for ΔAB V_T to Δtotal thoracoabdominal V_T was significantly greater within the IMT group (p=0.040) and significantly lower within the control group (p<0.001).

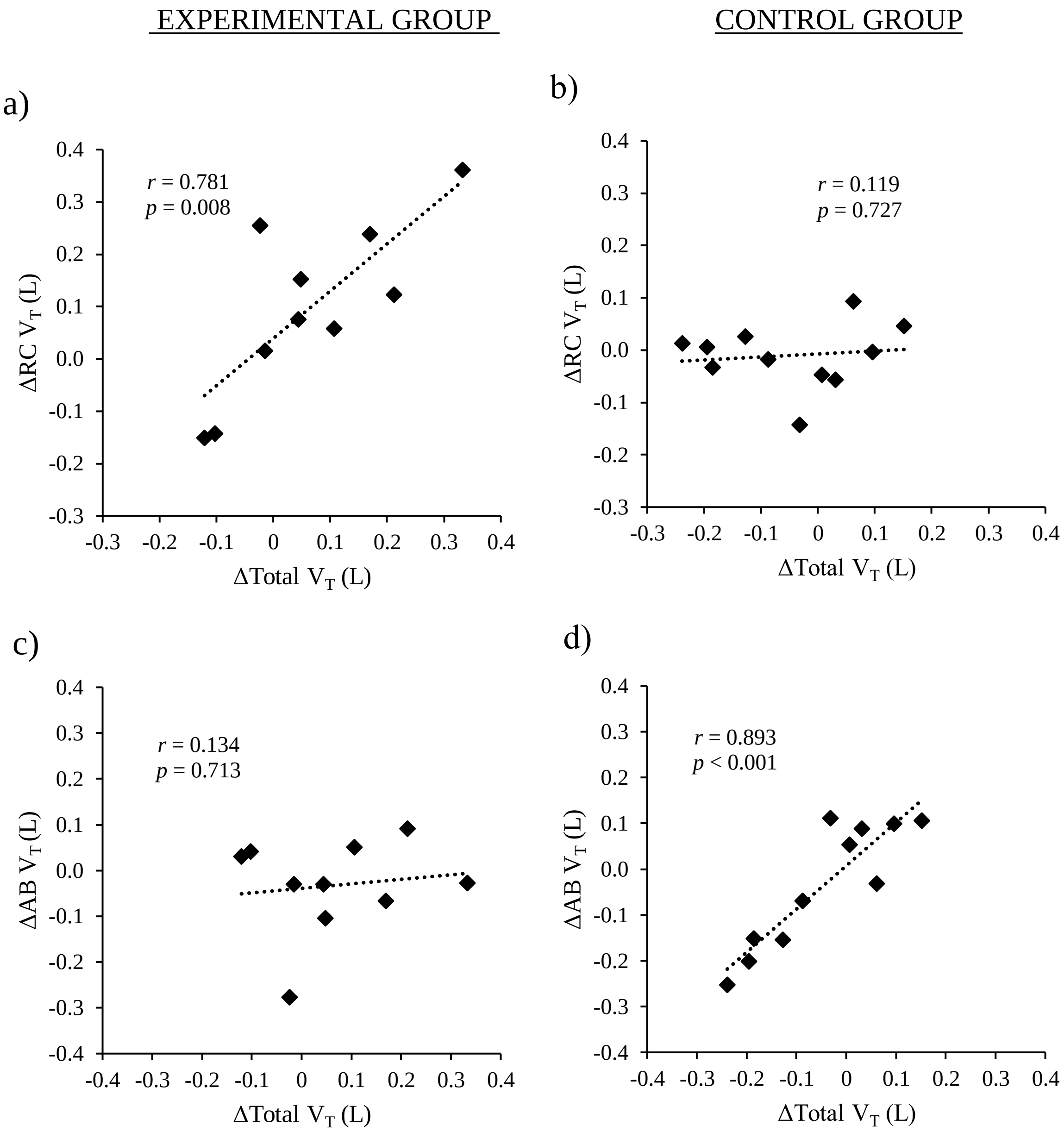


Figure 6-14. The association between delta (Δ) rib cage (RC) tidal volume (V_T) and Δtotal thoracoabdominal V_T (*a and b*), and between Δabdomen (AB) V_T and Δtotal thoracoabdominal V_T (*c and d*) within the IMT (*a and c*) and control (*b and d*) groups. Each data point represents the combined average values over exercise isotime (25%, 50%, 75%, and 100%) for each participant.

6.3.8. Central haemodynamic responses

Central haemodynamic responses at rest and during CWR exercise pre- and post-intervention are shown in figure 6-15. No significant intervention x pre-post x time interactions were observed for cardiac output (p=0.732, F=0.304), stroke volume (p=0.540, F=0.650), or heart rate (p=0.340, F=1.109).

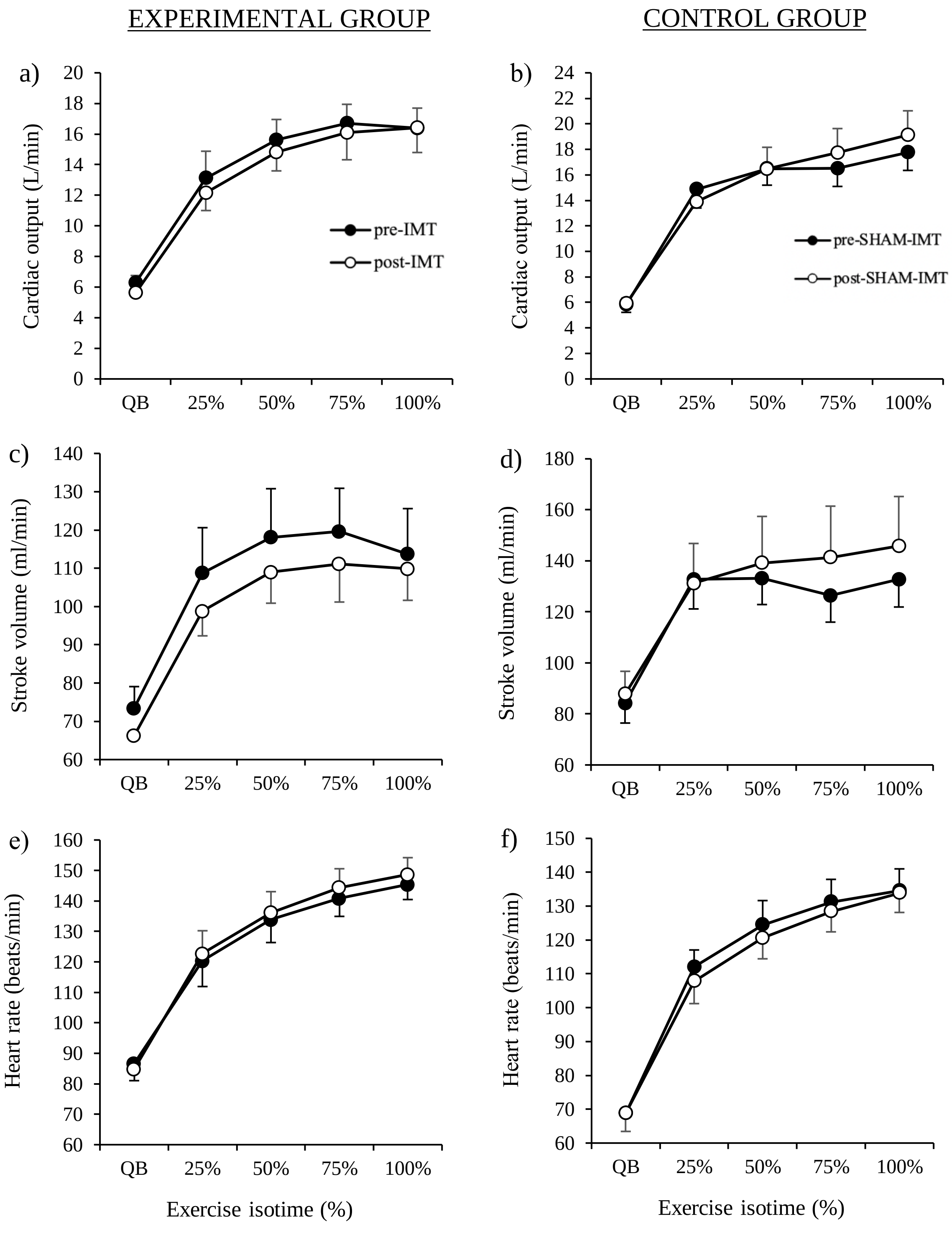


Figure 6-15. Cardiac output (*a and b*), stroke volume (*c and d*), and heart rate (*e and f*) responses during constant work rate exercise before (closed symbols) and after (open symbols) IMT in the experimental (*left panels*) and SHAM-IMT in the control groups (*right panels*). Data presented as mean ± SEM.

6.3.9. Physical activity levels

Significant intervention x pre-post interactions were observed for daily steps (p=0.012, F=7.766), vector magnitude counts (VMC; p=0.010, F=8.165), VMC/900 (p=0.010, F=8.165), sedentary time (p=0.018, F=6.745), and MVPA time (p=0.002, F=13.201; Table 6-4). These interactions were attributable to significant decreases following training within the control group only for daily steps (p=0.013), VMC (p=0.004), VMC/900 (p=0.004), and MVPA time (p<0.001), along with a significant decrease in sedentary time following training within the IMT group only (p=0.042).

6.3.10. Quality of life

No significant intervention x pre-post interactions were observed in any of the 8 dimensions of health (physical function: p=0.527, F=0.413; role physical: p=0.826, F=0.049; bodily pain: p=0.659, F=0.200; general health perception: 0.279, F=1.233; vitality: p=0.646, F=0.217; social function: p=0.307, F=1.096; role emotional: p=0.307, F=1.096; and mental health: p=0.443, F=0.612; Table 6-4). All dimensions remained unchanged following training in both the IMT and control groups.

6.3.11. Balance

No significant intervention x pre-post interactions were observed in any of the mini-BEST domains (anticipatory: p=0.401, F=0.736; reactive: p=0.162, F=2.100; sensory: p=0.952, F=0.004; dynamic: p=0.822, F=0.052; Table 6-4). A significant increase from pre-intervention values following training was observed for reactive postural control within the IMT group (p<0.001) but not within the control group (p=0.111). All other variables remained unchanged in both groups.

Table 6-4. Baseline and post-intervention values for physical activity, quality of life, and balance variables.

	IMT		Control	
	Baseline	Post-intervention	Baseline	Post-intervention
		Physical activity levels (Actigraph)		
Daily steps	9560 ± 3175	9847 ± 4262	11942 ± 2819	9128 ± 3678*†
VMC	568450 ± 124797	573515 ± 176688	599401 ± 91957	48218 ± 97383*†
VMC/900	631.6 ± 138.7	637.2 ± 196.3	666.0 ± 102.2	538..0 ± 108.2*†
Sedentary (min)	462.8 ± 35.3	434.8 ± 31.6*	426.4 ± 60.6	454.2 ± 69.2†
Light (min)	266.2 ± 56.2	245.7 ± 59.3	247.2 ± 64.6	239.5 ± 78.6
MVPA (min)	47.1 ± 30.9	50.5 ± 40.0	72.1 ± 24.8	41.0 ± 25.0*†
		Quality of life (SF-36)		
Physical function	90.5 ± 8.5	92.3 ± 5.2	93.3 ± 6.9	93.3 ± 6.5
Role physical	95.5 ± 15.1	95.5 ± 15.1	93.8 ± 15.5	95.8 ± 13.3
Bodily pain	87.7 ± 16.6	80.7 ± 26.7	86.9 ± 14.5	83.1 ± 11.7
General health perception	76.4 ± 8.7	74.5 ± 10.1	74.6 ± 9.9	75.8 ± 9.0
Vitality	70.9 ± 9.7	70.0 ± 7.4	65.8 ± 9.7	66.7 ± 8.1
Social function	98.9 ± 3.8	95.5 ± 8.4	93.7 ± 12.5	93.8 ± 11.3
Role emotional	93.9 ± 20.1	100.0 ± 0	97.2 ± 9.6	97.2 ± 9.6
Mental health	78.2 ± 7.0	77.5 ± 7.6	76.3 ± 8.8	73.7 ± 10.2
		Balance (mini-BEST)		
Anticipatory	5.1 ± 0.7	5.4 ± 0.5	5.3 ± 0.9	5.3 ± 0.8
Reactive	4.3 ± 0.8	5.5 ± 0.7*	4.0 ± 1.3	4.6 ± 1.8
Sensory	5.8 ± 0.4	5.9 ± 0.3	5.9 ± 0.3	6.0 ± 0.0
Dynamic	9.4 ± 0.7	9.2 ± 0.6	9.0 ± 0.9	8.9 ± 1.1

Data presented as mean±SD. MVPA, moderate to vigorous physical activity; VMC, vector magnitude count; *denote significant difference from pre-intervention; †significant intervention x pre-post interaction.

6.4. Discussion

The main findings of this chapter were that IMT resulted in significantly greater improvements in inspiratory muscle strength compared to SHAM-IMT. These improvements were associated with significantly greater 6MWD but not CWR endurance exercise time. Furthermore, breathing discomfort was reduced during 50% PI_{max} at 4 and 8 weeks of training in the IMT group. No significant changes were observed following training in total thoracoabdominal volume regulation during CWR exercise, however, greater changes in total V_T expansion during exercise were associated with greater changes in RC V_T within the IMT group only. This is indicative of greater inspiratory rib cage expansion and greater diaphragmatic descent post-IMT. Furthermore, IMT resulted in a significant reduction in sedentary time, however, all other changes in physical activity variables were due to changes within the control group only. Reactive postural control was significantly improved within the IMT group, and quality of life remained unchanged.

6.4.1. Effects of IMT on respiratory muscle function

Improvements in respiratory muscle strength (PI_{max}) observed in this chapter following IMT (~20 cmH_2O) are in line with previous studies in healthy older adults (outlined in chapter 3). The mechanisms explaining these improvements are likely increased inspiratory muscle strength, power output and speed of shortening (Romer & McConnell, 2003), and/or hypertrophy of inspiratory muscles (Mills et al., 2015; Souza et al., 2014). Furthermore, this chapter observed significantly reduced breathing discomfort following IMT during a bout of training at a given fraction (50%) of PI_{max} compared to the control group. This reduced effort perception may be explained by a combination of underlying mechanisms relating to structural and functional adaptations of the inspiratory muscles following IMT, including: 1) increased diaphragm thickness (Enright et al., 2006; Souza et al., 2014), 2) increased proportion of type I muscle fibres (Ramírez-Sarmiento et al., 2002), 3) increased oxidative capacity (Brown et al., 2012; Turner et al., 2012), 4) increased force-generating capacity (Romer et al., 2002a), and/or 5) desensitised sensory input from the inspiratory muscles to the brain (El-Manshawi, Killian, Summers, & Jones, 1986; Romer et al., 2002a). As no significant increases in respiratory muscle strength variables were observed within the control group, it is likely that the increased values within the IMT group can be explained by genuine increases in strength and not a placebo effect or improved technique of manoeuvres.

6.4.2. Effects of IMT on exercise capacity

A significant improvement in 6MWD (by 18.8 m) was observed in the IMT group following the 8-week intervention which was not evident in the control group (difference of −0.5 m). This finding is in line with previous studies outlined in chapter 3, showing significant improvement in 6MWD following IMT in healthy older adults (Huang et al., 2011; Rodrigues et al., 2018). No significant change in CWR exercise endurance time following IMT was observed within this study. To the authors knowledge, this is the first study to investigate the effects of IMT on sub-maximal cycling exercise tolerance in healthy older adults, however, these findings contrast with previous literature reporting increased endurance exercise time in COPD (Langer et al., 2018; Petrovic et al., 2012) and healthy younger individuals (Bailey et al., 2010; Edwards & Cooke, 2004).

6.4.3. Effects of IMT on breathing pattern and thoracoabdominal volume regulation

In the present study, no significant changes were observed in $\dot{V}_{\mathrm{E}}$ during CWR exercise following IMT. The findings presented for breathing pattern and thoracoabdominal volume regulation can, therefore, be viewed as both fractions of exercise isotime and relative to similar $\dot{V}_{\mathrm{E}}$ (ventilatory requirement) pre- and post-training (i.e., isoventilation). Previous studies in

COPD patients have reported changes in breathing pattern, specifically decreased ventilatory requirement and increased V_T, during exercise following respiratory muscle training interventions (Charususin et al., 2016; Koppers et al., 2006; Petrovic et al., 2012; Wanke et al., 1994). The advantage of this breathing pattern, reported by Koppers et al. (2006), include decreased ratio of dead space to V_T leading to an increase in effective alveolar ventilation, reduced WOB (Nici, 2000), and 3) delayed respiratory muscle fatigue, which would prevent a rapid, shallow breathing pattern being adopted (Larson & Kim, 1987). In the present study, no significant changes in breathing pattern or ventilatory requirement were observed in healthy older adults. This is in line with the study conducted by Langer et al. (2018) who observed an increased exercise capacity but no changes in breathing pattern or operational lung volumes in COPD patients.

The regression analysis within the current chapter implies that any increases in total V_T during sub-maximal exercise following training were associated with increased RC V_T and not increased AB V_V in the IMT group. Previous studies that have utilised measures of inspiratory muscle EMG have observed significantly greater activation of extradiaphragmatic muscles, such as the sternocleidomastoid, during PI_{max} manoeuvres post-IMT compared to a control group (Ando et al., 2020). As the estimated shear modulus of the diaphragm increased in both IMT and control groups within the study by Ando et al. (2020), the authors concluded that the increased EMG amplitudes, and thus improved neural factors, of the sternocleidomastoid could be one of the main mechanisms behind the greater improvement in PI_{max} observed within the IMT group. Furthermore, no changes in the EMG amplitude of the intercostal muscles were observed following IMT, with the authors suggesting that this may be either due to the length of the training programme (6 weeks) or the signal-to-noise ratio of measurements (Ando et al., 2020). Despite these findings, previous studies have reported no significant changes in extradiaphragmatic contribution during exercise following IMT in healthy young men (Ramsook et al., 2017). Furthermore, IMT has been found to reduce diaphragm activation (EMGdi) expressed relative to its maximum ($EMGdi/EMGdi_{max}$) in COPD patients (Langer et al., 2018). No significant changes in the ventilatory muscle recruitment index were reported however, leading the authors to conclude that the reduced EMGdi amplitude was not related to increased rib cage and accessory inspiratory muscle contribution resulting in diaphragm sparing (Langer et al., 2018).

The use of OEP to determine compartmental thoracoabdominal volume regulation following IMT has been reported at rest (Hoffman et al., 2021; Medeiros et al., 2019). The first of these studies (Medeiros et al., 2019) was conducted in chronic kidney disease patients, and involved an experimental group training at 50% PI_{max} for 8 weeks, with a control (sham) group training at the minimum device load (5 cmH_2O). The authors observed a significant increase of 0.1 L in RCp volume of the experimental group during IC manoeuvres following IMT compared to the control group. No difference, however, was observed during QB between groups. It was concluded that IMT was adequate to modify the volume of the chest cavity by directing the volume to the RCp compartment, altering the naturally restrictive pattern in chronic kidney disease patients (Medeiros et al., 2019). In the present study, a significant intervention x pre-post interaction was observed in the RCa compartment only when resting and all exercise time-points were combined, suggesting greater mobility of the lower rib cage, and potentially increased diaphragmatic descent. The significant association between changes in RC V_T and changes in total V_T suggest concurrent training adaptations of both the rib cage muscles and the diaphragm, which may result in the attenuation of the inspiratory muscle metaboreflex (Witt et al., 2007), reduced development of diaphragmatic fatigue and the maintenance of high V_T during exercise in order to avoid inefficient rapid shallow breathing (Illi, Hostettler, Mohler, Aliverti, & Spengler, 2011).

6.4.4. Effects of IMT on physical activity, balance, and quality of life

Sedentary time was decreased following IMT compared to the control group, with all other post-intervention changes in physical activity outcomes (daily steps, VMC, and MVPA) being attributed to decreased values within the control group. Research into the effect of IMT on physical activity levels in healthy older adults remains inconclusive. Aznar-Lain et al. (2007) reported an increase (~60%) in the levels of MVPA following IMT, alongside a decrease (~38%) within the control group. No other changes in physical activity measures, such as sedentary time, were observed, leading the authors to suggest that IMT may not increase the total quantity of physical activity but perhaps increase the quality (or intensity) of activities performed (Aznar-Lain et al., 2007). Furthermore, when measured via self-reported questionnaires (physical activity scale for the elderly), Mills et al. (2015) did not observe any changes in physical activity levels following IMT.

The improvement in reactive postural control following IMT in healthy older adults observed in the present chapter is supported by previous research that reported the greatest improvements within this domain of the mini-BEST measures (Ferraro et al., 2019). An increase in anticipatory postural adjustments, sensory orientation, and dynamic balance during gait was also reported in the study by Ferraro et al. (2019), however, this was not observed in the present chapter. The activation of the diaphragm during rapid limb movements (which challenges trunk stability) has previously been reported (Hodges & Gandevia, 2000a). This diaphragm activation assists with the mechanical stabilisation of the spine due to increased intra-abdominal pressure (Hodges & Gandevia, 2000b). Increased strength of the diaphragm (reflected by an increased PI_{max}) therefore, likely had a positive effect on reactive postural control (Ferraro et al., 2019).

No significant change in quality of life was observed in the present study. This is in contrast to the findings of (Huang et al., 2011) who found that a 6-week IMT intervention significantly improved five domains of the SF-36 (physical function, bodily pain, general health perception, vitality, and social function). This may be due to a ceiling effect within the present study as baseline scores were higher than those reported by Huang et al. (2011) in most of these domains (physical function: 90.5 vs 83.3; bodily pain: 87.7 vs 76.0; general health perception: 76.4 vs 70.2; and social function: 98.9 vs 75.0).

6.4.5. Study limitations and future directions

The relatively small sample size in the present chapter highlights the need for larger studies to be conducted in order to confirm the present findings. The difference in PI_{max} following IMT in older adults reported by Watsford and Murphy (2008) was used within the sample size calculation to consider changes in thoracoabdominal volume regulation arising due to improved inspiratory muscle strength, however, due to one drop-out, this study was slightly underpowered. Two familiarisation tests for the 6MWT are recommended to limit the learning effect in older adults (Kervio, Carre, & Ville, 2003), however, the participants in the present study performed only one at baseline and one at post-intervention.

Simultaneous measurements of EMGdi via multipair oesophageal catheters, as outlined previously (Jolley et al., 2009), or EMG of extradiaphragm muscles via surface EMG, were unavailable for the present study, meaning that respiratory muscle activation patterns could only be indirectly assessed via OEP. These measurements would have provided the opportunity to investigate $EMGdi/EMGdi_{max}$ as an index of neural respiratory drive, which has previously been found to decrease following IMT in COPD patients (Langer et al., 2018).

6.5. Conclusion

To conclude, this chapter has provided more evidence that IMT can significantly improve inspiratory muscle strength (as shown in previous studies outlined in chapter 3), as well as 6MWD (partly shown in chapter 3) in healthy older adults. Furthermore, this study observed significantly reduced breathing discomfort, which, along with the increased respiratory muscle strength suggests enduring physiological adaptations with IMT. This chapter employed OEP to address the thesis aim of investigating whether changes in thoracoabdominal volume regulation are observed during exercise following IMT. An increased RC and diaphragmatic contribution to V_T expansion during exercise was observed, suggesting a less restrictive effect on thoracic expansion, and increased diaphragmatic power generation. Whether or not this

IMT programme was well tolerated and/or the aforementioned changes in respiratory muscle function and exercise capacity were perceived by participants will be explored in the subsequent chapter.

CHAPTER 7 – OLDER ADULTS' PERSPECTIVES AND VIEWS ON INSPIRATORY MUSCLE TRAINING: A QUALITATIVE PERSPECTIVE

7.1. Introduction

Chapter 6 aimed to determine the effects of IMT on respiratory muscle strength, exercise capacity, thoracoabdominal volume regulation, and other quantitative measures of balance, physical activity, and quality of life. The purpose of the present chapter is to focus on qualitative measures of participants' perspectives and views towards this type of training programme.

The contribution of qualitative research is becoming more frequently used in clinical research in respect to exercise interventions and interventions based around improving quality of life. It is important when working with new devices/interventions that we assess participants' behavioural intention to use them in the future. By using a qualitative method, we can gain a wider understanding of participants' perspectives relating to these devices, and whether they have the intention to use them in the future. It is critical that we understand both positive and negative aspects of new devices and interventions if we want to establish them later in clinical practice and care.

Very few studies have employed qualitative methods of enquiry to explore participant perceptions towards IMT. Hoffman, Assis, Augusto, Silveira, and Parreira (2018) conducted semi-structured interviews with advanced lung disease patients following an 8-week IMT programme, regarding their perceptions of the training, their behaviour following training, as well as their mobility and daily activities. The participants within the study by Hoffman et al. (2018) reported improvements in daily activities, mobility, and communication, which were attributed to a perceived reduction in breathlessness. Furthermore, O'Connor, Lawson, Waterhouse, and Mills (2019) investigated the acceptability of IMT in COPD patients that had previously declined pulmonary rehabilitation. These patients found IMT to be acceptable and reported fewer barriers to IMT compared to pulmonary rehabilitation in regards to capability, opportunity, and motivation (O'Connor et al., 2019). In this group of patients, IMT was reported to hold greater value than pulmonary rehabilitation, with individuals more readily perceiving the value of targeting of inspiratory muscles to relieve breathlessness than exercising peripheral muscles (O’Connor et al., 2019). Positive perceptions of IMT have also been reported in stroke patients (de Menezes, Nascimento, Avelino, & Teixeira-Salmela, 2020). All patients within the study conducted by de Menezes et al. (2020) reported that they would recommend home-based IMT to other stroke patients, with 67% of patients very satisfied with the training, 33% satisfied, and none dissatisfied.

To the authors knowledge, there is currently no published research that has employed qualitative measures to explore participant view towards IMT in healthy older adults. This chapter, therefore, aims to determine the perspectives and views towards IMT, both immediately following the 8-week intervention in chapter 6 and at 3-months post training, as well as identify specific facilitators and barriers to IMT in this population. Participants from the control (SHAM-IMT) group in chapter 6 were also interviewed within this chapter to explore their perceptions and attitudes towards the “endurance” training and determine whether there was presence of a placebo effect.

7.2. Methods

7.2.1. Study design

This study adopted a qualitative design approach to determine perceptions and attitudes towards the 8-week IMT programme outlined in chapter 6. This study was approved by Northumbria University Newcastle Ethics Committee (No: 23701) and follows the consolidated criteria for reporting qualitative (COREQ) checklist (Tong, Sainsbury, & Craig, 2007) outlined below.

7.2.2. Research team and reflexivity

One member of the research team (JM) carried out interviews with the participants. JM currently holds a BSc (Hons) and MSc, with this work forming part of his PhD thesis. Throughout this PhD work, JM has accumulated knowledge on IMT in older adults by conducting a systematic review and meta-analysis on this topic (chapter 3), which may have resulted in the researcher having preordained desired responses from the interviews with the older adults in the present chapter.

7.2.3. Relationship with participants

JM had previous relationships with all participants within this chapter having tested them over the previous 8 weeks for chapter 6. All participants were aware that the interviews were to explore perspectives and views towards the 8-week IMT intervention in chapter 6. Participants were therefore aware of JM's research interests and the outcomes of studies being used to form a doctoral thesis. Due to JM being the lead researcher in both the present chapter and chapter 6, biases concerning researcher involvement and relationships with participants prior to interviews have been identified to ensure transparent reporting of findings. Specifically, JM was aware of the outcomes of participants following the 8-week IMT programme, and participants were aware that JM had observed participant familiarisation with training sessions and may have prior knowledge of their experiences.

7.2.4. Participant selection

Overall, 14 healthy older adults who participated in the IMT programme outlined in chapter 6 took part in this study. For the interviews immediately following the 8-week IMT intervention, the sample was comprised of 7 participants from the experimental (IMT) group and 7 participants from the control (SHAM-IMT) group. All participants were initially informed that they may be invited for interviews during the first visit of chapter 6 (and within the participant information sheet). A convenience sampling method was used as interviews were conducted on a first come, first serve basis. Following these interviews, the participants were provided with a debrief sheet (Appendix 10) and those in the control group were informed about the deception regarding the group being presented as “endurance” training to ensure adherence and placebo effect. Furthermore, these participants were recommended that, if they wanted to continue training, they should increase the intensity. Ten participants (5 in each group) answered follow-up questions at 3-months post-training. All participants provided written consent (Appendix 5) before the interviews.

7.2.5. Data collection

One-to-one semi-structured interviews with the participants. The initial interviews, aiming to explore participants’ attitudes, perceptions, and acceptability immediately following the 8-week IMT programme, were conducted face-to-face within the research laboratory at the end of their final visit outlined in chapter 6. Subsequent follow-up interviews were conducted over the phone. All interviews were audio recorded and later transcribed by the same researcher who had conducted the interviews (JM). There was no other presence of non-participants besides JM and the individual participants during interviews, field notes were not taken during interviews, and participants were not recruited on a data saturation basis.

This study used a range of open-ended questions to explore experiences and perceptions of the IMT programme, with the researcher following an interview schedule both immediately following the IMT programme (Table 7-1) and at 3-months follow-up (Table 7-2).

Table 7-1. Interview schedule immediately following the IMT programme.

Initial questions:	
1)	Had you heard of IMT before taking part in this study? If so, what had you heard? If not, did you have any idea of who might use these devices?
Experiences and acceptance:	
2)	Can you describe your experience with the training at home?
3)	Were there any aspects of the training you found easier?
4)	Were there any more or less enjoyable aspects to the training?
5)	Would you change anything about the training?
Perceived changes:	
6)	Have you noticed any changes in your exercise capacity/breathlessness since starting the training? If so, what sort of changes?
7)	Have you noticed any changes in your functional capacity around the house since starting the training? If so, what sort of changes?
8)	Have there been any changes in your engagement in physical activity since starting the training? If so, what sort of changes?
9)	Have you noticed any changes in your balance since starting the training? If so, what sort of changes?
10)	Have you noticed any changes in your quality of life since starting the training? If so, what sort of changes?
Engagement in physical activity:	
11)	How often do you exercise a week?
12)	What sort of exercise do you usually do?
13)	How fit would you say you are compared to the average person your age?
Closing questions:	
14)	Do you plan to keep using the device now that the study is over?
15)	Would you recommend this inspiratory muscle training programme?

Table 7-2. Interview schedule for 3-months post-IMT follow-up.

Initial questions:	
1)	Have you used the IMT device since the study ended?
If so:	
2)	Are you currently still using the IMT device? How long did you use it for?
3)	Are you still doing the same protocol as set in the study? (30 breaths, twice a day) If not, what are you doing now?/what were your reasons for adjusting the protocol?
4)	Why do you think you have continued to use the IMT device?
5)	Have there been any changes in your exercise capacity since finishing the 8-week IMT within the study? If so, what sort of changes?
If not:	
6)	What are the reasons that you stopped training with the IMT device?
7)	What, if anything, could have made you continue training with the IMT device?
8)	Have you noticed any changes in your exercise capacity since you stopped training?

7.2.6. Data analysis

Data was analysed by following the six phases of deductive thematic analysis (Braun & Clarke, 2006). This included: 1) familiarisation (transcribing interviews and noting initial ideas), 2) generating initial codes (all transcripts were uploaded into NVivo 12 [QSR International] for the coding of interesting features by JM), 3) searching for themes (gathering all data relevant to each potential theme), 4) reviewing themes (JM and GB reviewed themes to ensure credibility and trustworthiness of findings), 5) defining and naming themes (research team meetings with JM and GB were conducted to discuss codes and generate clear definitions for each theme) and 6) producing the report (vivid, compelling extract examples were selected to be included within the study; Braun & Clarke, 2006). Participants are identified by training group (IMT or control; C) and interview number. Quotations are presented within themes to demonstrate findings. Results relating to the perceived changes following IMT in the experimental group were displayed in a word cloud by using a free online word cloud generator (wordclouds.com). Words that appear more frequently in the source data have greater prominence in the word cloud. Example transcripts are included in Appendix 11.

7.3. Results

The findings of the initial interviews immediately following the IMT programme within this study were grouped into three thematic categories: 1) “experience and attitudes towards IMT”, 2) “perceived changes following IMT”, and 3) “perceptions of physical activity levels”. The first two themes included specific sub-themes: “facilitators to IMT”, and “barriers to IMT” within theme 1, and “exercise capacity”, “breathlessness”, “balance”, and “quality of life” within theme 2 (Table 7-3).

The perceptions of the participants interviewed 3-months following the IMT programme were grouped into three thematic categories: “facilitators to maintaining IMT”, barriers to maintaining IMT”, and “perceived changes following IMT” (Table 7-4).

Table 7-3. Themes and sub-themes within the initial interviews.

Initial interviews	
Themes	**Sub-themes**
Experience and attitudes towards IMT	Facilitators to IMT
	Barriers to IMT
Perceived changes following IMT	Exercise capacity
	Breathlessness
	Balance
	Quality of life
Perceptions of physical activity levels	

Table 7-4. Themes within the follow-up interviews.

Follow-up interviews
Themes
Facilitators to maintaining IMT
Barriers to maintaining IMT
Perceived changes following IMT

7.3.1. Interviews immediately following the IMT intervention

7.3.1.1 Experience and attitudes towards IMT

The majority of participants within both the IMT and control group reported a positive experiences with the IMT programme, reporting specific facilitators including that the training was easy and was not time consuming.

> *"The training, I thought it was fairly easy to fit into the day. Because being retired, it wasn't time consuming or anything like that [...] it wasn't particularly onerous"* IMT04 (SC)

Some participants stated the importance of a routine when training at home.

> *"It was just remembering that I had to do it but then it got into a routine which was good" IMT*02 (CF)

> *"You know, did it first thing in the morning then did it at tea time, twice a day just to get into a routine [...] and once I got into a routine I found it quite easy to do "* C05 (MB)

> *"I had to devise a rigid programme and stick to it. I found for the first few days, I was 'oh I'll do it later on, I'll do it later on' but after two or three days I was doing it religiously, 8 o'clock every morning and (laughs) just after tea every evening. So I was organised and routinised"* C06 (AW)

Participants reported enjoying the training or taking an interest in what they were doing.

> *"I really enjoyed it. It was interesting doing the breathing every morning and every night [...] I found it fascinating to see just how far I could push myself"* IMT01 (EF)

> *"I think it's been really interesting doing the training [...] Just quite interested and willing to do it really"* IMT03 (PB)

Two participants within the control group, however, reported negative experiences with the training, stating specific barriers including that it felt like a chore or it was not particularly interesting.

> *"It was a bit of a chore towards the end. In the beginning it was new and exciting but towards the end it was becoming a bit of a chore"* C01 (DG)

> *"Er it was interesting for the first 2 weeks then it got a bit monotonous"* C02 (MS)

This is likely due to the inability for participants within the control group to adjust the intensity of the training over the course of the 8 weeks.

> *"I think because I knew I was going to be doing exactly the same thing for 8 weeks, that's when it wasn't particularly interesting. I think if I'd have known it was going to increase week on week or whatever then it would have been more interesting"* C02 (MS)

> *"It might have been challenging to change the level maybe [...] perhaps just to give it more of a challenge [...] it would have been nice to have upped the ante a bit"* C03 (VP)

Other barriers to training included discomfort with the mouthpiece and difficulty keeping count of the breaths.

> *"My mouth used to get very dry after using the device. To be honest, 30 breaths was enough at the end [...] it started to get a bit uncomfortable"* C04 (MG)

> *"I wasn't too happy with the breathing apparatus at home, simply because I felt the mouthpiece was a little bit too big for my mouth"* IMT06 EJ

> *"I didn't enjoy the breathing into the apparatus very much but I knew I had to do it [...] keeping count was quite difficult"* IMT03 PB

7.3.1.2. Perceived changes following IMT

Four out of seven participants within the IMT group, along with three out of seven participants within the control group reported perceived improvements in exercise capacity. Figure 7-1 shows the results from the word cloud from source data relating to questions regarding perceived changes following IMT.

Figure 7-1. Word cloud relating to perceived changes following IMT in the experimental group.

These improvements were primarily associated with walking, and particularly when walking up stairs or hills.

> *"[…] even walking at pace now I'm nowhere near as panting for breath or thinking 'hang on I better slow down because I'm struggling for breath' as I used to […] but walking capacity, yes, I would say there has been a difference"* IMT04 (SC)
>
> *"If you were to ask me if I did see an improvement, I think it was going up a flight of stairs […] quite often I'm going to the top to the roof car park and struggling a bit and actually I think that was easier. So maybe yes I did see an improvement"* IMT03 (PB)

> *"[...] there's one place with a lot of stairs we have to go up and I'm very poor on stairs and I found I was getting to the top of the stairs easier than I was before"* C03 (VP)

Some participants attributed their perceived improvements in exercise capacity to reduced breathlessness or more controlled breathing.

> *"When I'm at the gym my breathing's a lot better [...] more controlled, whereas before I would breathe at the wrong time [...] and I think it's a little bit stronger. I don't get out of breath as much as I used to because I think I'm controlling my breathing properly rather than just grasping at it"* IMT01 (EF)

> *"I was cutting things back and writhing at things [whilst gardening] and I had no problem whatsoever where previous I might have been a bit puffing [...] definitely improved, definitely much better"* IMT02 (CF)

> *"I used to, after a reasonable length of time walking or exercising, I used to notice a slight wheeze [...] and now I haven't got that anymore"* C01 (DG)

When asked about any changes in exercise capacity following IMT, one participant attributed their perceived lack of effect to already having a strong baseline level of fitness.

> *"Erm... no. I must admit, I find it difficult to say because I'm fairly active, so you know, from having that sort of base level to start with I just continued as normal basically"* C05 (MB)

The majority of participants reported no perceived change in their balance following IMT, with only one participant in each group stating that they thought it had improved.

> *"To me it feels better. I can stand longer on one leg"* C04 (MG)

No participant reported any changes in quality of life over the 8-week IMT programme, with the exception of one participant suggesting that the new challenge may have had a slight effect.

> *"It hasn't really made a huge difference. The only thing is, it's given me a challenge to do something different and that has improved my quality of life in that respect"* C03 (VP)

7.3.1.3. Perceptions of physical activity levels

Nearly all participants reported that they perceived themselves to be fitter than the average person their age. Two participants (one in each group) stated that they thought they were about average in terms of fitness, and one participant in the control group was unsure. The most common type of physical activity that participants engaged in was walking, with other activities such as cycling, yoga, exercise classes, swimming, golf, and running also being reported. Participants reported exercising at least 3 times a week with the majority walking every day.

7.3.2. Follow-up interviews at 3-months post IMT intervention

All participants apart from one within the control group reported using the IMT device at least once since finishing the 8-week intervention. Within the IMT group, one participant reported that they trained with the device every day, one reported training occasionally (3–4 times a week), two reported that they had initially continued training but this had gradually tailed off, and one reported that they had stopped training initially but then started again after a period of time. Within the control group, one participant reported training with the device often, one reported training very occasionally, two initially continued training and then stopped, and one reported not training at all.

All participants within the IMT group reported following the exact same protocol that they had performed during the 8-week intervention (30 breaths, twice daily). For the participants in the control group that had continued using the device, two reported following the same protocol but increased the intensity, one reported decreasing the training to 20 breaths whilst also keeping the same intensity, stating that:

> *"I found it easier obviously because I was doing 20 […] but I think I probably could go up in intensity a little bit definitely […] I thought now I wasn't actually testing it I could make it a little bit easier for myself really"* C03 (VP)

The final participant that continued to use the IMT device after the 8-week intervention reported changing the protocol to 60 breaths, once a day, at the same intensity performed during the intervention. Their reason for adjusting the training protocol was mainly due to convenience and time-saving.

> *"Just convenience really I think. […] Just the routine I got into I suppose. I used to do it first thing and I used to do it after tea. But I suppose after tea I've got into a habit of lounging and not doing it […] yeah convenience and time-saving"* C06 (AW)

7.3.2.1. Facilitators to maintaining IMT

When asked the reasons why participants had chosen to continue with IMT, one of the main facilitators to IMT at 3-months follow-up was if the participants had reported perceived benefits during the initial 8-week intervention.

> *"I found that it helped with my breathing and certainly with going to the gym, it controlled the way I breathed. So doing exercise was better because I was actually more conscious of how I breathed"* IMT01 (EF)

> *"Well just on the logic that it was doing me some good and I accepted the philosophy behind that it was improving my lung capacity and my endurance so to speak"* C06 (AW)

Participants in the control group that reported perceived benefits after 8-weeks reported continuing IMT at a higher intensity to see if these benefits continued.

> *"Yeah, I found during the course of the trial I found that my breath was better, I was breathing better […] so I put it up thinking that it would have, continue having an effect. And in my opinion, as unscientific as it is, it has"* C04 (MG)

> *"I thought it would help. I don't know if it was a psychological thing but I actually felt that it did help me a little bit when I was walking up a hill or steps […] so I thought I would try it a little bit longer on a higher rate to see if it helped any"* C01 (DG)

One participant highlighted the convenience of IMT which allowed them to partake in a different form of exercise when they were unable to go to the gym.

> *"[…] if I wasn't going to the gym it was a way of doing aerobic exercise without having to actually physically exert and go to the gym and lift weights […] it allows us to carry on with some kind of aerobic exercise rather than missing it out completely […] so it fills in on, say if the weather's bad or if you're pushed for time and you can't really get there that day"* IMT04 (SC)

Another participant stated that they started IMT again after being diagnosed with acute costochondritis and out of curiosity that it would help with their breathing.

> *"[…] I saw the POWERbreathe on the floor […] and I thought 'breathing', I'm going to try that and it really has helped"* IMT02 (CF)

7.3.2.2. Barriers to maintaining IMT

Common barriers to IMT following the initial 8-week intervention in both groups were the participants struggling to find the time, especially with external factors 'overtaking' the training in terms of level of importance.

> *"[…] I know it doesn't take a lot of time but you just get other distractions […] so other things overtook it"* IMT04 (SC)

> *"It was purely time. It was finding the time because I had a lot of things going on in family life. And it was just trying to fit it in and remember to do it when other things overtook it"* C01 (DG)

> *"We've got a new grandson and there's a lot going on and just finding the time"* IMT03 (PB)

Various external factors were also reported to have broken up the routine that participants were initially in during the intervention.

> *"[…] when I stopped using it, it coincided with me going away for a week. We went away and by the time we got back, I was doing a bit of work and stuff and I wasn't back in a routine. Then something else happened […] where you're doing something that broke up the sequence […] if you don't have it as a regular routine you just tend to forget"* IMT05 (MO)

> *"[…] it became part of routine then routine changed with external reasons. Erm and then I went back to it and then the holiday happened"* C04 (MG)

One participant reported that the barriers to continuing IMT were the combination of being busy and forgetting.

> *"I forget, basically, I forget. […] I mean well and then I think oh dash I've forgotten to do that again today. […] I'm always busy and I've always got to be somewhere and erm it's just a combination of forgetting and being busy I would say"* C03 (VP)

Another participant stated their perceived importance of external motivation to continue training.

> *"[…] I'm very much a team player, I don't do many things just on my own, I like to be part of a group. […] Even just your phone call now has made me think you know why did I put it down? […] I like to be motivated by others"* IMT03 (PB)

The participant that did not continue to use the device at all explained that this was due to not perceiving any beneficial effect over the course of the 8-week intervention.

> *"Well to be perfectly honest, I wasn't- I didn't feel in myself that between starting the process and ending it whether I felt any vast improvement or benefit in sort of how I was living my life"* C05 (MB)

7.3.2.3. Perceived changes at 3-months follow-up

In those that continued with IMT after the 8-week intervention, some participants reported perceived changes in exercise capacity and breathlessness.

> *"[…] I thought that my breathing was better, my overall strength with breathing was better. I just felt it was really beneficial and certainly because I do a lot of walking, I can pace myself better"* IMT01 (EF)
>
> *"The improvement I made during it [8-week intervention] erm I think I can still feel that. […] It's not so much, you know, when you're first on [the bike] but I think it just gives you that- you feel as though you're not getting out of breath as quickly […] I can do things at a slightly higher level"* IMT05 (MO)
>
> *"[…] when I go on the treadmill I know that I can increase the speed on the actual ramp whereas before I used to, not struggle, but start to get out of breath and sweating. There was a difference there that I could increase the speed on the treadmill without thinking that oh this is really hard now"* IMT04 (SC)
>
> *"I breathe better, I don't have shortage of breath. I never really did but less so if that makes sense?* C04 (MG)

Some participants who continued to use the IMT device did not perceive any further changes in exercise capacity or breathlessness, suggesting that this may be due to them engaging in a lot of physical activity already.

> *"[…] it would be difficult to isolate the POWERbreathe […] as the variable […] I do quite a bit of swimming and cycling […] so I wouldn't say I could measure any noticeable difference.* C06 (AW)
>
> *"I walk a lot anyway and I try to walk quickly so I don't really have a problem anyway so it was difficult to say there was any improvement […] I can't say I've noticed any difference but it didn't do any harm"* IMT03 (PB)

7.4. Discussion

This chapter aimed to explore perceptions of IMT in healthy older adults both immediately following the 8-week intervention outlined in chapter 6 and at 3-months follow-up and is the first study to employ qualitative methods to determine attitudes, as well as barriers and facilitators to training in this population. The main themes that emerged from the interviews immediately following the intervention were: experience and attitudes towards IMT (including sub-themes of facilitator and barriers to IMT), perceived changes following IMT (including exercise capacity, breathlessness, balance, and quality of life), and perceptions of physical activity levels. The themes arising from interviews at 3-months follow up were: facilitators to maintaining IMT, barriers to maintaining IMT, and perceived changes at 3-months follow-up.

The majority of participants reported a positive experience with IMT, with facilitators including that the device was easy to use and the sessions were not time-consuming. This is in line with previous qualitative studies that aimed to determine the perceptions of IMT in patients with COPD (O'Connor et al., 2019). The participants in the study conducted by O'Connor et al. (2019) had previously declined pulmonary rehabilitation and instead, took part in an initial 8-week training intervention consisting of 30 breaths, twice a day, 5 days per week with weekly supervision and reassessment of $PI_{max.}$ After 8 these 8 weeks, participants were advised to continue training unsupervised, twice daily, 3 times per week, for a further 18 weeks (until 6-month follow-up). Specific facilitators to IMT such as the development of a routine reinforcing the participants' behaviour observed by O'Connor et al. (2019) both at baseline and reiterated at 6-months follow-up was also found to be a key facilitator within the present study. Previous literature has also highlighted the role of habit or routine as an important factor in sustaining long-term adherence to physical activity interventions (Martin & Woods, 2012). Furthermore, home-based activities have been associated with higher adherence to prescribed physical activity than facility-based activities (Leijon et al., 2010), with the authors suggesting that relatively simple home-based activities may more easily become habits than complex behaviours.

The home-based environment has indeed been identified as a facilitator to IMT in COPD (O'Connor et al., 2019) and stroke patients (de Menezes et al., 2020). These patients reported liking that they could participate in the training in their own home, especially due to weather conditions (O'Connor et al., 2019), and preferred this setting over physiotherapy clinics due to being more comfortable and being able to fit exercises into their daily routine (de Menezes et al., 2020). Within the present study, the training environment could be seen to be a less important facilitating factor to IMT in healthy older adults compared to diseased populations, with only one participant highlighting the convenience of the home-based setting especially when they were unable to partake in other forms of facility-based physical activity such as the gym. Conversely, when asked if anything could have made them continue IMT, another participant reported that they like to be part of a group and to be motivated by others.

The few negative experiences reported with the training were related to perceived issues with the device itself (mouthpiece too big), or a lack of interest with the training. Interestingly, it was only participants within the control group that perceived the training to be a chore and is likely due to the lack of training progression within this group. The SHAM-IMT fixed training intensity ($<15\%$ PI_{max}) has also been used in previous studies (Craighead et al., 2021; Langer et al., 2018; Mills et al., 2015) as a placebo-control. Furthermore, SHAM-IMT was presented to those in the control group as 'endurance training' to ensure full placebo effect and to ensure participants were blinded to the real purpose of the study (Goosey-Tolfrey, Foden, Perret, & Degens, 2010; Langer et al., 2018). As participants within the control group of the present study were unable to adjust the training intensity, they were more likely to perceive no training progress which has previously been reported as a barrier to continuing exercise programmes (Tak, Van Uffelen, Paw, van Mechelen, & Hopman-Rock, 2012).

Some participants in the present study reported improved exercise capacity and reduced sensations of breathlessness, supporting previous findings in COPD patients (Hoffman et al., 2018). The perceived changes during the initial 8-week intervention was found to be a key facilitator to maintaining IMT in healthy older adults, with those that reported benefits immediately after the 8-weeks being more likely to continue training. This was also true for individuals within the control group that performed SHAM-IMT, with two individuals reporting that they perceived benefits during the 8-week intervention and therefore increased the intensity after 8-weeks to see if these benefits continued. Those that did not report perceived changes in exercise capacity or breathlessness tended to attribute the lack of effect to having high baseline physical activity levels, implying that they perceived IMT to be insufficient at improving exercise capacity.

7.5. Conclusion

This chapter has addressed the thesis aim of exploring older adults’ views towards IMT by utilising qualitative methods of enquiry (semi-structured interviews), thus providing us with a wider understanding regarding participant perspectives and behavioural intentions towards these types of devices. The findings of this chapter suggest that IMT is well tolerated in healthy older adults, with the majority of participants reporting positive experiences with the training programme. Perceived changes following training reported by some participants were related to improved exercise capacity and reduced breathlessness. These perceived changes during the initial 8-week intervention were an important facilitator to maintaining IMT.

CHAPTER 8 – GENERAL DISCUSSION

8.1. Overview

The overall aim of this thesis was to investigate the effect of IMT in healthy older adults. Chapter 3 explored the current literature surrounding this topic and assessed the strength of the evidence in regards to improving inspiratory muscle strength and functional capacity. Chapter 5 investigated the acute thoracoabdominal volume, and gas exchange responses to TFRL at low, medium, and high intensities, and, specifically, age-related differences in these variables between healthy younger and older adults. The chronic effects an 8-week IMT programme in older adults were investigated in chapter 6 - specifically, on respiratory muscle strength, exercise capacity, and thoracoabdominal volume regulation during rest and exercise. Secondary measures of physical activity, balance, and quality of life were also investigated within chapter 6. Finally, chapter 7 explored the perspectives and views towards the IMT programme performed by participants in chapter 6 both immediately following training and at 3-months post-training.

8.2. Summary of main findings

The systematic review and meta-analysis in chapter 3 found that IMT can significantly increase inspiratory muscle strength by ~23 cmH_2O in healthy older adults. Importantly, this chapter observed no significant association between baseline PI_{max} and IMT-induced improvements in PI_{max} which is in contrast to earlier research that have observed greater improvements in subgroups of COPD (Basso-Vanelli et al., 2016; Gosselink et al., 2011) and CHF patients (Montemezzo et al., 2014) with respiratory muscle weakness. In terms of exercise capacity, this chapter determined an average improvement in the 6MWD by ~25 m which can be classified as a relatively small, albeit clinically important difference (Perera et al., 2006); however, the meta-analysis did not reach the level of statistical significance, highlighting the need for further studies investigating the effects of IMT on exercise capacity in a healthy ageing population.

The experimental chapters within this thesis utilised OEP to investigate whether acute inspiratory muscle loading (chapter 5) and IMT (chapter 6) alters the behaviour of the respiratory muscles, reflected by changes in compartmental thoracoabdominal volume regulation. The investigation of thoracoabdominal volume regulation during acute bouts of TFRL at low, medium, and high intensities (30, 50, and 70% PI_{max} respectively) within chapter 5 were in line with previous research (da Fonsêca et al., 2019; da Fonsêca et al., 2020) that has observed increases in V_{EI}, and decreases in V_{EE} during inspiratory muscle loading compared to resting levels. Importantly, decreases in total V_{EE} below FRC during TFRL were mainly due to decreases in the AB compartment in both younger and older adults, and tended to further decrease with increased intensity of TFRL.

In regards to age-related differences, chapter 5 showed that younger adults exhibited significantly greater RC V_T expansion during high intensities (50 and 70% PI_{max}) compared to their older counterparts, a finding also observed during pressure-threshold loading (de Souza et al., 2016). Furthermore, younger adults had significantly greater regression slopes for the RC muscle contribution, and significantly lower slopes for AB contribution, to total V_T expansion at all levels of TFRL compared to older adults. This likely reflects the physiological changes to the respiratory system during the healthy ageing process outlined in chapter 2, including reduced elastic recoil of the lung and reduced compliance of the chest wall. An increased contribution of the RCa was observed at all intensities of TFRL compared to resting values in both age groups in chapter 5, a finding also observed by (de Souza et al., 2016) during pressure-threshold loading at 40% PI_{max}.

Based on the conclusions from chapter 3 and 5, chapter 6 investigated whether repeated bouts of inspiratory muscle loading (in the form an 8-week IMT programme) improves respiratory muscle strength and exercise capacity in healthy older adults, and whether increases in strength of the respiratory muscles translate into long-lasting changes in thoracoabdominal volume regulation during rest and exercise. The IMT programme within chapter 6 incorporated the most commonly used protocol determined in chapter 3 (30 breaths, twice daily, at 50% PI_{max}), with participants who performed IMT in the experimental group showing significantly improved inspiratory muscle strength, reduced respiratory muscle discomfort at a given fraction of PI_{max}, and increased 6MWD compared to the control group. As no changes were observed in the absolute values for $\dot{V}_E$ during CWR cycling exercise following training, pre- and post-intervention breathing pattern and thoracoabdominal volume regulation variables were, therefore, considered as fractions of exercise isotime (or external work rate) and relative to similar ventilatory requirement pre- and post-training (i.e., isoventilation). Changes in total V_T expansion during CWR exercise following IMT was principally associated with RC V_T expansion in the experimental group, which was not the case in the control group, potentially suggesting that IMT resulted in greater compliance of the RC compartment along with improved diaphragm force generation.

Finally, this thesis explored older adults' perspectives and views towards IMT (chapter 7) both immediately following the 8-week intervention (chapter 6) and at 3-months follow-up. The majority of participants reported positive experiences towards the IMT intervention, with individuals highlighting specific facilitating factors including ease of use, the short amount of time needed to perform training, and the importance of routine. The home-based environment in the present thesis may be considered less of an important facilitator to IMT in healthy older adults compared to in COPD (O'Connor et al., 2019) and stroke patients (de Menezes et al., 2020), with only one participant highlighting the convenience of the home-based setting. A key facilitator to maintaining IMT at 3-months follow-up was the perceived beneficial changes during the initial 8-week intervention, with those that reported perceived benefits after 8-weeks being more likely to continue training. These changes were primarily associated with improved exercise capacity and reduced breathlessness, in line with previous findings in COPD patients (Hoffman et al., 2018) and supporting the increased 6MWD observed following IMT in chapter 6. The perceived reductions in breathlessness did not however, translate into reduced Borg scale ratings for dyspnoea during CWR exercise in chapter 6.

Key barriers to IMT were also identified in chapter 7 and included the training feeling like a chore or that training was not particularly interesting. This was mainly reported in the control group and may be explained by the inability for this group to progress in terms of intensity over the 8 weeks.

8.3. Strengths, limitations, and future directions

The use of state-of-the-art OEP technology within this thesis allowed for the non-invasive measurement of both total and compartmental thoracoabdominal volume regulation at rest, during inspiratory muscle loading, as well as being the first to investigate IMT-related changes in these variables during exercise. Future research could expand on the initial findings from chapter 6 of the current thesis by investigating IMT-related changes in thoracoabdominal volumes and breathing pattern variables during eucapnic voluntary hyperpnoea (EVH), reproducing the ventilatory requirements experienced by participants during moderate and intense exercise. The use of locomotor muscles during cycling compared to EVH has shown that at a given level of ventilatory requirement, breathing pattern, and WOB, there is greater contribution from the expiratory abdominal muscles (Vogiatzis et al., 2010). The absence of locomotor muscle involvement during EVH would allow for any changes in total and compartmental thoracoabdominal volumes following IMT to be directly attributable to structural and/or functional adaptations of the respiratory muscles.

The different IMT devices used across chapters could be considered a limitation of this thesis. A TFRL device was used by participants within chapter 5 to determine acute thoracoabdominal volume responses to inspiratory muscle loading, however, due to financial constraints participants used a less expensive pressure-threshold loading device within chapter 6 to determine the long-lasting thoracoabdominal volume responses to IMT. Furthermore, use of a TFRL device allowed for the accurate determination of intensities as fractions of PI_{max} (via an LCD screen) to be performed by the participants within chapter 5, making this study highly reproducible, and would not be possible if using a pressure-threshold device. This inconsistency therefore limits conclusions as to how a number of acute bouts of training may lead to long-lasting effects on thoracoabdominal volumes during exercise. As an IMT programme with a TFRL device has been found result in greater improvements in inspiratory muscle strength, endurance, power, and shortening velocity, along with greater tolerance of higher training loads in COPD patients compared to IMT with a pressure-threshold loading device (Langer et al., 2015), future IMT research should employ this training technique to determine whether this is the case for healthy older adults. Although recent research have reported no significant change in thoracoabdominal volume regulation measured via OEP at rest following TFRL in COPD patients (Hoffman et al., 2021), the effects on these variables during exercise remain unknown.

As the majority of data collection for this thesis took place during 2021, the coronavirus (COVID-19) pandemic had significant effects on participant recruitment and ethical considerations. In order to reduce the risks associated with COVID-19 vulnerability, the age range within the inclusion criteria was set between 60–70 years with an ethical amendment later submitted to extend this to between 60–75 years due to the speed of the vaccine rollout. Furthermore, the majority of participants in chapter 7 perceived themselves to be fitter than the average person their age. Future research should aim to determine the effects of IMT in older populations (>75 years) where inspiratory muscle weakness (i.e. PI_{max} <70% predicted normal) may be more pronounced (Enright et al., 1994; Watsford et al., 2007). In weaker individuals, IMT may have more favourable effects of exercise capacity than those with stronger baseline PI_{max} as observed in COPD (Gosselink et al., 2011) and CHF patients (Montemezzo et al., 2014).

Long-COVID patients may also benefit from this method of training due to this population presenting with reduced inspiratory muscle strength (Hennigs et al., 2021), with recent research observing significant improvements in respiratory muscle strength, estimated $\dot{V}O_2$ max, and perceived breathlessness following an 8-week IMT programme (McNarry et al., 2022). In particular relevance to this thesis, LoMauro, Gervasoni, Andreoli, and Aliverti (2021) have utilised OEP to determine ventilatory patterns at rest and during vital capacity manoeuvres in long-COVID patients. The authors observed a restrictive pattern entirely located in the RCp compartment (LoMauro et al., 2021). It would be interesting to investigate whether IMT induces any significant changes in thoracoabdominal volume regulation within this particular population, given that in the current thesis, post-IMT total V_T expansion was significantly associated with RC V_T expansion.

8.4. Clinical implications

This thesis provides further evidence that IMT may be an important intervention in geriatric care. Inspiratory muscle weakness in older adults may lead to pulmonary dysfunction (Buchman et al., 2008a), and is associated with reduced mobility (Buchman et al., 2008b) and physical performance (Watsford et al., 2007). Important findings from this thesis include significant improvements in respiratory muscle strength, breathing discomfort, and exercise capacity following IMT in older adults, with the majority of participants reporting positive experiences and perceived benefits to training. Most IMT devices are relatively cheap, and can be performed in a home-based setting without the need for supervision, highlighting the cost-effectiveness of this intervention.

References

Aaron, E., Seow, K., Johnson, B., & Dempsey, J. (1992). Oxygen cost of exercise hyperpnea: implications for performance. *Journal of Applied Physiology, 72*(5), 1818-1825.

Agostoni, E., & d'Angelo, E. (1985). Statics of the chest wall. *Lung biology in health and disease, 29*, 259-295.

Agostoni, E., & Rahn, H. (1960). Abdominal and thoracic pressures at different lung volumes. *Journal of Applied Physiology, 15*(6), 1087-1092.

Ahmed, T., Steward, J. A., & O'Mahony, M. S. (2012). Dyspnoea and mortality in older people in the community: a 10-year follow-up. *Age and Ageing, 41*(4), 545-549.

Albuquerque, I. M. d., Rossoni, C. S., Cardoso, D. M., Paiva, D. N., & Fregonezi, G. (2013). Effects of short inspiratory muscle training on inspiratory muscle strength and functional capacity in physically active elderly: A quasi-experimental study. *The European Journal of Physiotherapy, 15*(1), 11-17.

Aliverti, A. (2008). Lung and chest wall mechanics during exercise: effects of expiratory flow limitation. *Respiratory physiology & neurobiology, 163*(1-3), 90-99.

Aliverti, A. (2016). The respiratory muscles during exercise. *Breathe, 12*(2), 165-168.

Aliverti, A., Cala, S., Duranti, R., Ferrigno, G., Kenyon, C., Pedotti, A., . . . Yan, S. (1997). Human respiratory muscle actions and control during exercise. *Journal of Applied Physiology, 83*(4), 1256-1269.

Aliverti, A., Dellacà, R., Pelosi, P., Chiumello, D., Gattinoni, L., & Pedotti, A. (2001). Compartmental analysis of breathing in the supine and prone positions by optoelectronic plethysmography. *Annals of biomedical engineering, 29*(1), 60-70.

Aliverti, A., & Pedotti, A. (2002). Opto-electronic plethysmography. In *Mechanics of breathing* (pp. 47-59): Springer.

Aliverti, A., & Pedotti, A. (2014). Optoelectronic plethysmography: principles of measurements and recent use in respiratory medicine. In *Mechanics of Breathing* (pp. 149-168): Springer.

Ambrosino, N., Opasich, C., Crotti, P., Cobelli, F., Tavazzi, L., & Rampulla, C. (1994). Breathing pattern, ventilatory drive and respiratory muscle strength in patients with chronic heart failure. *European Respiratory Journal, 7*(1), 17-22.

Ando, R., Ohya, T., Kusanagi, K., Koizumi, J., Ohnuma, H., Katayama, K., & Suzuki, Y. (2020). Effect of inspiratory resistive training on diaphragm shear modulus and accessory inspiratory muscle activation. *Applied Physiology, Nutrition, and Metabolism, 45*(8), 851-856.

Anthonisen, N., Danson, J., Robertson, P. C., & Ross, W. (1969). Airway closure as a function of age. *Respiration physiology, 8*(1), 58-65.

ATS/ERS statement on respiratory muscle testing. (2002). ATS/ERS Statement on respiratory muscle testing. *Am J Respir Crit Care Med, 166*, 518-624.

Aznar-Lain, S., Webster, A., Cañete, S., San Juan, A. F., Mojares, L. L., Pérez, M., . . . Chicharro, J. (2007). Effects of inspiratory muscle training on exercise capacity and spontaneous physical activity in elderly subjects: a randomized controlled pilot trial. *International journal of sports medicine, 28*(12), 1025-1029.

Babb, T., & Rodarte, J. (2000). Mechanism of reduced maximal expiratory flow with aging. *Journal of Applied Physiology, 89*(2), 505-511.

Babcock, M., Pegelow, D., McClaran, S., Suman, O., & Dempsey, J. (1995). Contribution of diaphragmatic power output to exercise-induced diaphragm fatigue. *Journal of Applied Physiology, 78*(5), 1710-1719.

Babcock, M. A., Pegelow, D. F., Harms, C. A., & Dempsey, J. A. (2002). Effects of respiratory muscle unloading on exercise-induced diaphragm fatigue. *Journal of Applied Physiology, 93*(1), 201-206.

Babcock, M. A., Pegelow, D. F., Taha, B. H., & Dempsey, J. A. (1998). High frequency diaphragmatic fatigue detected with paired stimuli in humans. *Medicine and science in sports and exercise, 30*(4), 506-511.

Bailey, S. J., Romer, L. M., Kelly, J., Wilkerson, D. P., DiMenna, F. J., & Jones, A. M. (2010). Inspiratory muscle training enhances pulmonary O2 uptake kinetics and high-intensity exercise tolerance in humans. *Journal of Applied Physiology*.

Balzamo, E., Lagier-Tessonnier, F., & Jammes, Y. (1992). Fatigue-induced changes in diaphragmatic afferents and cortical activity in the cat. *Respiration physiology, 90*(2), 213-226.

Bardsley, P., Bentley, S., Hall, H., Singh, S., Evans, D., & Morgan, M. (1993). Measurement of inspiratory muscle performance with incremental threshold loading: a comparison of two techniques. *Thorax, 48*(4), 354-359.

Basso-Vanelli, R. P., Di Lorenzo, V. A. P., Labadessa, I. G., Regueiro, E. M., Jamami, M., Gomes, E. L., & Costa, D. (2016). Effects of inspiratory muscle training and calisthenics-and-breathing exercises in COPD with and without respiratory muscle weakness. *Respiratory care, 61*(1), 50-60.

Bastianini, F., Schena, E., & Silvestri, S. (2012). *Accuracy evaluation on linear measurement through opto-electronic plethysmograph.* Paper presented at the 2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society.

Beaumont, M., Forget, P., Couturaud, F., & Reychler, G. (2018). Effects of inspiratory muscle training in COPD patients: A systematic review and meta-analysis. *The clinical respiratory journal, 12*(7), 2178-2188.

Bernstein, D. P. (1986). A new stroke volume equation for thoracic electrical bioimpedance: theory and rationale. *Critical care medicine, 14*(10), 904-909.

Bioengineering, B. (2011). Optoelectronic plethysmography compedium marker setup; a handbook about marker positioning on subjects in standing and supine positions. *Brooklyn, BTS Bioengineering*.

Black, L. F., & Hyatt, R. E. (1969). Maximal respiratory pressures: normal values and relationship to age and sex. *American Review of Respiratory Disease, 99*(5), 696-702.

Borg, G. A. (1982). Psychophysical bases of perceived exertion. *Medicine & science in sports & exercise*.

Bougault, V., Lonsdorfer-Wolf, E., Charloux, A., Richard, R., Geny, B., & Oswald-Mammosser, M. (2005). Does thoracic bioimpedance accurately determine cardiac output in COPD patients during maximal or intermittent exercise? *Chest, 127*(4), 1122-1131.

Brandão, D. C., Lage, S. M., Britto, R. R., Parreira, V. F., de Oliveira Jr, W. A., Martins, S. M., . . . Alcoforado, L. (2012). Chest wall regional volume in heart failure patients during inspiratory loaded breathing. *Respiratory physiology & neurobiology, 180*(2-3), 269-274.

Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. *Qualitative research in psychology, 3*(2), 77-101.

Brazier, J. E., Harper, R., Jones, N., O'cathain, A., Thomas, K., Usherwood, T., & Westlake, L. (1992). Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *British medical journal, 305*(6846), 160-164.

Brischetto, M., Millman, R., Peterson, D., Silage, D., & Pack, A. (1984). Effect of aging on ventilatory response to exercise and CO2. *Journal of Applied Physiology, 56*(5), 1143-1150.

Britto, R. R., Zampa, C. C., De Oliveira, T. A., Prado, L. F., & Parreira, V. F. (2009). Effects of the aging process on respiratory function. *Gerontology, 55*(5), 505-510.

Brown, P. I., Sharpe, G. R., & Johnson, M. A. (2008). Inspiratory muscle training reduces blood lactate concentration during volitional hyperpnoea. *European journal of applied physiology, 104*(1), 111-117.

Brown, P. I., Sharpe, G. R., & Johnson, M. A. (2012). Inspiratory muscle training abolishes the blood lactate increase associated with volitional hyperpnoea superimposed on exercise and accelerates lactate and oxygen uptake kinetics at the onset of exercise. *European journal of applied physiology, 112*(6), 2117-2129.

Bruschi, C., Cerveri, I., Zoia, M. C., Fanfulla, F., Fiorentini, M., Casali, L., . . . Grassi, C. (1992). Reference Values of Maximal Respiratory Mouth Pressures: A Population-based Study1-3. *Am Rev Respir Dis, 146*, 790-793.

Buchman, A., Boyle, P., Wilson, R., Gu, L., Bienias, J. L., & Bennett, D. (2008a). Pulmonary function, muscle strength and mortality in old age. *Mechanisms of ageing and development, 129*(11), 625-631.

Buchman, A., Boyle, P., Wilson, R., Leurgans, S., Shah, R., & Bennett, D. (2008b). Respiratory muscle strength predicts decline in mobility in older persons. *Neuroepidemiology, 31*(3), 174-180.

Caine, M., & McConnell, A. (1998). *Pressure threshold inspiratory muscle training improves submaximal cycling performance.* Paper presented at the Third Annual Conference of the European College of Sport Science.

Caine, M., & McConnell, A. (2000). Development and evaluation of a pressure threshold inspiratory muscle trainer for use in the context of sports performance. *Sports Engineering, 3*(3), 149-160.

Cala, S., Kenyon, C., Ferrigno, G., Carnevali, P., Aliverti, A., Pedotti, A., . . . Rochester, D. (1996). Chest wall and lung volume estimation by optical reflectance motion analysis. *Journal of Applied Physiology, 81*(6), 2680-2689.

Cebria i Iranzo, M., Arnall, D. A., Igual Camacho, C., & Tomas, J. M. (2014). Effects of inspiratory muscle training and yoga breathing exercises on respiratory muscle function in institutionalized frail older adults: a randomized controlled trial. *J Geriatr Phys Ther, 37*(2), 65-75. doi:10.1519/JPT.0b013e31829938bb

Cebria i Iranzo, M. A., Balasch-Bernat, M., Tortosa-Chuliá, M. Á., & Balasch-Parisi, S. (2018). Effects of Resistance Training of Peripheral Muscles Versus Respiratory Muscles in Older Adults With Sarcopenia Who are Institutionalized: A Randomized Controlled Trial. *Journal of aging and physical activity, 26*(4), 637-646.

Charloux, A., Lonsdorfer-Wolf, E., Richard, R., Lampert, E., Oswald-Mammosser, M., Mettauer, B., . . . Lonsdorfer, J. (2000). A new impedance cardiograph device for the non-invasive evaluation of cardiac output at rest and during exercise: comparison with the “direct” Fick method. *European journal of applied physiology, 82*(4), 313-320.

Charususin, N., Gosselink, R., Decramer, M., Demeyer, H., McConnell, A., Saey, D., . . . Heijdra, Y. F. (2018). Randomised controlled trial of adjunctive inspiratory muscle training for patients with COPD. *Thorax, 73*(10), 942-950.

Charususin, N., Gosselink, R., McConnell, A., Demeyer, H., Topalovic, M., Decramer, M., & Langer, D. (2016). Inspiratory muscle training improves breathing pattern during exercise in COPD patients. *European Respiratory Journal, 47*(4), 1261-1264.

Chen, H.-I., & Kuo, C.-S. (1989). Relationship between respiratory muscle function and age, sex, and other factors. *Journal of Applied Physiology, 66*(2), 943-948.

Chen, R., Que, C., & Yan, S. (1998). Introduction to a new inspiratory threshold loading device. *European Respiratory Journal, 12*(1), 208-211.

Chen, Z., Eldridge, F. L., & Wagner, P. G. (1992). Respiratory-associated thalamic activity is related to level of respiratory drive. *Respiration physiology, 90*(1), 99-113.

Chiappa, G. R., Roseguini, B. T., Vieira, P. J., Alves, C. N., Tavares, A., Winkelmann, E. R., . . . Ribeiro, J. P. (2008). Inspiratory muscle training improves blood flow to resting and exercising limbs in patients with chronic heart failure. *Journal of the American College of Cardiology, 51*(17), 1663-1671.

Chihara, K., Kenyon, C. M., & Macklem, P. T. (1996). Human rib cage distortability. *Journal of Applied Physiology, 81*(1), 437-447.

Cho, J.-E., Lee, H.-J., Kim, M.-K., & Lee, W.-H. (2018). The improvement in respiratory function by inspiratory muscle training is due to structural muscle changes in patients with stroke: a randomized controlled pilot trial. *Topics in stroke rehabilitation, 25*(1), 37-43.

Cooper, B. G., Stocks, J., Hall, G. L., Culver, B., Steenbruggen, I., Carter, K. W., . . . Ruppel, G. (2017). The Global Lung Function Initiative (GLI) Network: bringing the world's respiratory reference values together. *Breathe, 13*(3), e56-e64.

Craighead, D. H., Heinbockel, T. C., Freeberg, K. A., Rossman, M. J., Jackman, R. A., Jankowski, L. R., . . . D'Alessandro, A. (2021). Time-Efficient Inspiratory Muscle Strength Training Lowers Blood Pressure and Improves Endothelial Function, NO Bioavailability, and Oxidative Stress in Midlife/Older Adults With Above-Normal Blood Pressure. *Journal of the American Heart Association, 10*(13), e020980.

Crapo, R., Morris, A., Clayton, P., & Nixon, C. (1982). Lung volumes in healthy nonsmoking adults. *Bulletin europeen de physiopathologie respiratoire, 18*(3), 419-425.

da Fonsêca, J., Resqueti, V., Benício, K., Fregonezi, G., & Aliverti, A. (2019). Acute Effects of Inspiratory Loads and Interfaces on Breathing Pattern and Activity of Respiratory Muscles in Healthy Subjects. *Frontiers in Physiology, 10,* 993-993.

da Fonsêca, J. D. M., Aliverti, A., Benício, K., de Farias Sales, V. S., da Cunha Lima, L. F. S., Resqueti, V. R., & de Freitas Fregonezi, G. A. (2022). Breathing pattern and muscle activity using different inspiratory resistance devices in children with MBS. *ERJ Open Research*.

da Fonsêca, J. D. M., Resqueti, V. R., Benício, K., de Farias Sales, V. S., da Cunha Lima, L. F. S., Aliverti, A., . . . de Freitas Fregonezi, G. A. (2020). Effects of Inspiratory Load on Chest Wall Kinematics, Breathing Pattern, and Respiratory Muscle Activity of Mouth-Breathing Children. *Respiratory care, 65*(9), 1285-1294.

Da Gama, A. E. F., de Andrade Carvalho, L., Feitosa, L. A., do Nascimento Junior, J. F., da Silva, M. G. N. M., Amorim, C. F., . . . de Andrade, A. D. (2013). Acute effects of incremental inspiratory loads on compartmental chest wall volume and predominant activity frequency of inspiratory muscle. *Journal of electromyography and kinesiology, 23*(6), 1269-1277.

Dall'Ago, P., Chiappa, G. R., Guths, H., Stein, R., & Ribeiro, J. P. (2006). Inspiratory muscle training in patients with heart failure and inspiratory muscle weakness: a randomized trial. *Journal of the American College of Cardiology, 47*(4), 757-763.

de Menezes, K. K. P., Nascimento, L. R., Avelino, P. R., & Teixeira-Salmela, L. F. (2020). Benefits of Home-Based Respiratory Muscle Training from the Perspectives of Individuals Who Had a Stroke: Qualitative Study. *PM&R, 12*(10), 990-996.

de Souza, H. M., Rocha, T., Campos, S. L., Brandão, D. C., Fink, J. B., Aliverti, A., & de Andrade, A. D. (2016). Acute effects of different inspiratory efforts on ventilatory pattern and chest wall compartmental distribution in elderly women. *Respiratory physiology & neurobiology, 227*, 27-33.

De Troyer, A., & Boriek, A. M. (2011). Mechanics of the respiratory muscles. *Comprehensive Physiology, 1*(3), 1273-1300.

De Troyer, A., & Estenne, M. (1984). Coordination between rib cage muscles and diaphragm during quiet breathing in humans. *Journal of Applied Physiology, 57*(3), 899-906.

De Troyer, A., & Estenne, M. (1988). Functional anatomy of the respiratory muscles. *Clinics in chest medicine, 9*(2), 175-193.

De Troyer, A., Kirkwood, P. A., & Wilson, T. A. (2005). Respiratory action of the intercostal muscles. *Physiological reviews, 85*(2), 717-756.

Decramer, M. (1997). Hyperinflation and respiratory muscle interaction. *European Respiratory Journal, 10*(4), 934-941.

Decramer, M., & De Troyer, A. (1984). Respiratory changes in parasternal intercostal length. *Journal of Applied Physiology, 57*(4), 1254-1260.

Dellacà, R. L., Aliverti, A., Pelosi, P., Carlesso, E., Chiumello, D., Pedotti, A., & Gattinoni, L. (2001). Estimation of end-expiratory lung volume variations by optoelectronic plethysmography. *Critical care medicine, 29*(9), 1807-1811.

DeLorey, D., & Babb, T. (1999). Progressive mechanical ventilatory constraints with aging. *American Journal of Respiratory and Critical Care Medicine, 160*(1), 169-177.

Demeyer, H., Burtin, C., Van Remoortel, H., Hornikx, M., Langer, D., Decramer, M., . . . Troosters, T. (2014). Standardizing the analysis of physical activity in patients with COPD following a pulmonary rehabilitation program. *Chest, 146*(2), 318-327.

Demeyer, H., Mohan, D., Burtin, C., Vaes, A. W., Heasley, M., Bowler, R. P., . . . Frei, A. (2021). Objectively measured physical activity in patients with COPD: recommendations from an international task force on physical activity. *Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation, 8*(4), 528.

Dempsey, J. A., La Gerche, A., & Hull, J. H. (2020). Is the healthy respiratory system built just right, overbuilt, or underbuilt to meet the demands imposed by exercise? *Journal of Applied Physiology, 129*(6), 1235-1256.

Dempsey, J. A., Romer, L., Rodman, J., Miller, J., & Smith, C. (2006). Consequences of exercise-induced respiratory muscle work. *Respiratory physiology & neurobiology, 151*(2-3), 242-250.

Dominelli, P. B., Guenette, J. A., Wilkie, S. S., Foster, G. E., & Sheel, A. W. (2011). Determinants of expiratory flow limitation in healthy women during exercise. *Med Sci Sports Exerc, 43*(9), 1666-1674.

Downey, A. E., Chenoweth, L. M., Townsend, D. K., Ranum, J. D., Ferguson, C. S., & Harms, C. A. (2007). Effects of inspiratory muscle training on exercise responses in normoxia and hypoxia. *Respiratory physiology & neurobiology, 156*(2), 137-146.

Duron, B. (1981). Intercostal and diaphragmatic muscle endings and afferents. *Regulation of breathing, 17*(part I), 473-540.

Edwards, A., & Cooke, C. (2004). Oxygen uptake kinetics and maximal aerobic power are unaffected by inspiratory muscle training in healthy subjects where time to exhaustion is extended. *European journal of applied physiology, 93*(1), 139-144.

El-Manshawi, A., Killian, K., Summers, E., & Jones, N. (1986). Breathlessness during exercise with and without resistive loading. *Journal of Applied Physiology, 61*(3), 896-905.

Enright, P. L., Kronmal, R. A., Manolio, T. A., Schenker, M. B., & Hyatt, R. E. (1994). Respiratory muscle strength in the elderly. Correlates and reference values. Cardiovascular Health Study Research Group. *American Journal of Respiratory and Critical Care Medicine, 149*(2), 430-438.

Enright, S., Chatham, K., Ionescu, A. A., Unnithan, V. B., & Shale, D. J. (2004). Inspiratory muscle training improves lung function and exercise capacity in adults with cystic fibrosis. *Chest, 126*(2), 405-411.

Enright, S. J., Unnithan, V. B., Heward, C., Withnall, L., & Davies, D. H. (2006). Effect of high-intensity inspiratory muscle training on lung volumes, diaphragm thickness, and exercise capacity in subjects who are healthy. *Physical therapy, 86*(3), 345-354.

Fadel, P. J., Wang, Z., Watanabe, H., Arbique, D., Vongpatanasin, W., & Thomas, G. D. (2004). Augmented sympathetic vasoconstriction in exercising forearms of postmenopausal women is reversed by oestrogen therapy. *The Journal of physiology, 561*(3), 893-901.

Faisal, A., Webb, K. A., Guenette, J. A., Jensen, D., Neder, J. A., O'Donnell, D. E., & Network, C. R. R. (2015). Effect of age-related ventilatory inefficiency on respiratory sensation during exercise. *Respiratory physiology & neurobiology, 205*, 129-139.

Ferraro, F. V., Gavin, J. P., Wainwright, T., & McConnell, A. (2019). The effects of 8 weeks of inspiratory muscle training on the balance of healthy older adults: a randomized, double-blind, placebo-controlled study. *Physiological reports, 7*(9), e14076.

Ferrigno, G., Borghese, N., & Pedotti, A. (1990). Pattern recognition in 3D automatic human motion analysis. *ISPRS Journal of Photogrammetry and Remote Sensing, 45*(4), 227-246.

Franchignoni, F., Horak, F., Godi, M., Nardone, A., & Giordano, A. (2010). Using psychometric techniques to improve the Balance Evaluation System's Test: the mini-BESTest. *Journal of rehabilitation medicine: official journal of the UEMS European Board of Physical and Rehabilitation Medicine, 42*(4), 323.

Frank, N. R., Mead, J., & Ferris, B. (1957). The mechanical behavior of the lungs in healthy elderly persons. *The Journal of clinical investigation, 36*(12), 1680-1687.

Gandevia, S., & Macefield, G. (1989). Projection of low-threshold afferents from human intercostal muscles to the cerebral cortex. *Respiration physiology, 77*(2), 203-214.

Geddes, E. L., O'Brien, K., Reid, W. D., Brooks, D., & Crowe, J. (2008). Inspiratory muscle training in adults with chronic obstructive pulmonary disease: an update of a systematic review. *Respiratory medicine, 102*(12), 1715-1729.

Gething, A., Williams, M., & Davies, B. (2004). Inspiratory resistive loading improves cycling capacity: a placebo controlled trial. *British journal of sports medicine, 38*(6), 730-736.

Gigliotti, F. (2010). Mechanisms of dyspnea in healthy subjects. *Multidisciplinary respiratory medicine, 5*(3), 1-7.

Gilbert, R., Auchincloss Jr, J., Brodsky, J., & Boden, W. a. (1972). Changes in tidal volume, frequency, and ventilation induced by their measurement. *Journal of Applied Physiology, 33*(2), 252-254.

Godi, M., Franchignoni, F., Caligari, M., Giordano, A., Turcato, A. M., & Nardone, A. (2013). Comparison of reliability, validity, and responsiveness of the mini-BESTest and Berg Balance Scale in patients with balance disorders. *Physical therapy, 93*(2), 158-167.

Gomes-Neto, M., Saquetto, M. B., Silva, C. M., Carvalho, V. O., Ribeiro, N., & Conceicao, C. S. (2016). Effects of respiratory muscle training on respiratory function, respiratory muscle strength, and exercise tolerance in patients poststroke: a systematic review with meta-analysis. *Archives of physical medicine and rehabilitation, 97*(11), 1994-2001.

Goosey-Tolfrey, V., Foden, E., Perret, C., & Degens, H. (2010). Effects of inspiratory muscle training on respiratory function and repetitive sprint performance in wheelchair basketball players. *British journal of sports medicine, 44*(9), 665-668.

Gosselink, R., De Vos, J., Van Den Heuvel, S., Segers, J., Decramer, M., & Kwakkel, G. (2011). Impact of inspiratory muscle training in patients with COPD: what is the evidence? *European Respiratory Journal, 37*(2), 416-425.

Gosselink, R., Troosters, T., & Decramer, M. (2000). Distribution of muscle weakness in patients with stable chronic obstructive pulmonary disease. *Journal of Cardiopulmonary Rehabilitation and Prevention, 20*(6), 353-360.

Graham, B. L., Steenbruggen, I., Miller, M. R., Barjaktarevic, I. Z., Cooper, B. G., Hall, G. L., . . . McCormack, M. C. (2019). Standardization of spirometry 2019 update. An official American thoracic society and European respiratory society technical statement. *American Journal of Respiratory and Critical Care Medicine, 200*(8), e70-e88.

Griffiths, L. A., & McConnell, A. K. (2007). The influence of inspiratory and expiratory muscle training upon rowing performance. *European journal of applied physiology, 99*(5), 457-466.

Guenette, J. A., & Jensen, D. (2014). Aging and sex differences. *Dyspnea: Mechanisms, Measurement and Management. 3rd ed. London, New York: CRC Press/Tailor & Francis*, 25-38.

Guenette, J. A., Witt, J. D., McKenzie, D. C., Road, J. D., & Sheel, A. W. (2007). Respiratory mechanics during exercise in endurance-trained men and women. *The Journal of physiology, 581*(3), 1309-1322.

HajGhanbari, B., Yamabayashi, C., Buna, T. R., Coelho, J. D., Freedman, K. D., Morton, T. A., . . . Sheel, A. W. (2013). Effects of respiratory muscle training on performance in athletes: a systematic review with meta-analyses. *The Journal of Strength & Conditioning Research, 27*(6), 1643-1663.

Häkkinen, K., Newton, R. U., Gordon, S. E., McCormick, M., Volek, J. S., Nindl, B. C., . . . Häkkinen, A. (1998). Changes in muscle morphology, electromyographic activity, and force production characteristics during progressive strength training in young and older men. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 53*(6), B415-B423.

Hamberger, G. (1749). De Respirationis Mechanismo et usu genuino. *Iena: Christoph Croeker, 1749*.

Han, J., Gayan-Ramirez, G., Dekhuijzen, R., & Decramer, M. (1993). Respiratory function of the rib cage muscles. *European Respiratory Journal, 6*(5), 722-728.

Harik-Khan, R. I., Wise, R. A., & Fozard, J. L. (1998). Determinants of maximal inspiratory pressure: the Baltimore Longitudinal Study of Aging. *American Journal of Respiratory and Critical Care Medicine, 158*(5), 1459-1464.

Harms, C. A. (2007). Insights into the role of the respiratory muscle metaboreflex. *The Journal of physiology, 584*(Pt 3), 711.

Harms, C. A., Babcock, M. A., McClaran, S. R., Pegelow, D. F., Nickele, G. A., Nelson, W. B., & Dempsey, J. A. (1997). Respiratory muscle work compromises leg blood flow during maximal exercise. *Journal of Applied Physiology, 82*(5), 1573-1583.

Harms, C. A., Wetter, T. J., McClaran, S. R., Pegelow, D. F., Nickele, G. A., Nelson, W. B., . . . Dempsey, J. A. (1998). Effects of respiratory muscle work on cardiac output and its distribution during maximal exercise. *Journal of Applied Physiology, 85*(2), 609-618.

Hart, E. C., Charkoudian, N., Wallin, B. G., Curry, T. B., Eisenach, J., & Joyner, M. J. (2011). Sex and ageing differences in resting arterial pressure regulation: the role of the β-adrenergic receptors. *The Journal of physiology, 589*(21), 5285-5297.

Henke, K. G., Sharratt, M., Pegelow, D., & Dempsey, J. A. (1988). Regulation of end-expiratory lung volume during exercise. *Journal of Applied Physiology, 64*(1), 135-146.

Hennigs, J. K., Huwe, M., Hennigs, A., Oqueka, T., Simon, M., Harbaum, L., . . . Addo, M. M. (2021). Respiratory Muscle Dysfunction in COVID-19 Patients with Persistent Symptoms.

Higgins, J. P., & Green, S. (2011). *Cochrane handbook for systematic reviews of interventions* (Vol. 4): John Wiley & Sons.

Hill, J. M. (2000). Discharge of group IV phrenic afferent fibers increases during diaphragmatic fatigue. *Brain research, 856*(1-2), 240-244.

Hill, K., Jenkins, S., Philippe, D., Cecins, N., Shepherd, K., Green, D., . . . Eastwood, P. (2006). High-intensity inspiratory muscle training in COPD. *European Respiratory Journal, 27*(6), 1119-1128.

Hill, K., Jenkins, S. C., Hillman, D. R., & Eastwood, P. R. (2004). Dyspnoea in COPD: can inspiratory muscle training help? *Australian Journal of physiotherapy, 50*(3), 169-180.

Ho, S. F., O'Mahony, M. S., Steward, J. A., Breay, P., Buchalter, M., & Burr, M. L. (2001). Dyspnoea and quality of life in older people at home. *Age and Ageing, 30*(2), 155-159.

Hodges, P. W., & Gandevia, S. C. (2000a). Activation of the human diaphragm during a repetitive postural task. *The Journal of physiology, 522*(1), 165-175.

Hodges, P. W., & Gandevia, S. C. (2000b). Changes in intra-abdominal pressure during postural and respiratory activation of the human diaphragm. *Journal of Applied Physiology, 89*(3), 967-976.

Hoffman, M., Assis, M. G., Augusto, V. M., Silveira, B. M. F., & Parreira, V. F. (2018). The effects of inspiratory muscle training based on the perceptions of patients with advanced lung disease: a qualitative study. *Brazilian Journal of Physical Therapy, 22*(3), 215-221.

Hoffman, M., Vieira, D. S., Silveira, B. M., Augusto, V. M., & Parreira, V. F. (2021). Effects of inspiratory muscle training on resting breathing pattern in patients with advanced lung disease. *Respiratory physiology & neurobiology, 283*, 103560.

Holland, A. E., Spruit, M. A., Troosters, T., Puhan, M. A., Pepin, V., Saey, D., . . . Pitta, F. (2014). An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *European Respiratory Journal, 44*(6), 1428-1446.

Horak, F. B., Wrisley, D. M., & Frank, J. (2009). The balance evaluation systems test (BESTest) to differentiate balance deficits. *Physical therapy, 89*(5), 484-498.

Huang, C.-H., Yang, G.-G., Wu, Y.-T., & Lee, C.-W. (2011). Comparison of inspiratory muscle strength training effects between older subjects with and without chronic obstructive pulmonary disease. *Journal of the Formosan Medical Association, 110*(8), 518-526.

Hudson, A. L., Butler, J. E., Gandevia, S. C., & De Troyer, A. (2010). Interplay between the inspiratory and postural functions of the human parasternal intercostal muscles. *Journal of neurophysiology, 103*(3), 1622-1629.

Iandelli, I., Aliverti, A., Kayser, B., Dellacà, R., Cala, S. J., Duranti, R., . . . Yan, S. (2002). Determinants of exercise performance in normal men with externally imposed expiratory flow limitation. *Journal of Applied Physiology, 92*(5), 1943-1952.

Illi, S. K., Held, U., Frank, I., & Spengler, C. M. (2012). Effect of respiratory muscle training on exercise performance in healthy individuals. *Sports medicine, 42*(8), 707-724.

Illi, S. K., Hostettler, S., Mohler, E., Aliverti, A., & Spengler, C. M. (2011). Compartmental chest wall volume changes during volitional normocapnic hyperpnoea. *Respiratory physiology & neurobiology, 177*(3), 294-300.

Janssens, J.-P. (2005). Aging of the respiratory system: impact on pulmonary function tests and adaptation to exertion. *Clinics in chest medicine, 26*(3), 469-484.

Janssens, J.-P., Pache, J.-C., & Nicod, L. (1999). Physiological changes in respiratory function associated with ageing. *European Respiratory Journal, 13*(1), 197-205.

Jensen, D., Ofir, D., & O'Donnell, D. E. (2009). Effects of pregnancy, obesity and aging on the intensity of perceived breathlessness during exercise in healthy humans. *Respiratory physiology & neurobiology, 167*(1), 87-100.

Jensen, L. A., Onyskiw, J. E., & Prasad, N. (1998). Meta-analysis of arterial oxygen saturation monitoring by pulse oximetry in adults. *Heart & lung, 27*(6), 387-408.

Johnson, B., Reddan, W., Seow, K., & Dempsey, J. (1991a). Mechanical constraints on exercise hyperpnea in a fit aging population. *American Review of Respiratory Disease, 143*(5 I), 968-977.

Johnson, B. D., Babcock, M. A., Suman, O. E., & Dempsey, J. A. (1993). Exercise-induced diaphragmatic fatigue in healthy humans. *The Journal of physiology, 460*(1), 385-405.

Johnson, B. D., Badr, M. S., & Dempsey, J. A. (1994). Impact of the aging pulmonary system on the response to exercise. *Clinics in chest medicine, 15*(2), 229-246.

Johnson, B. D., Reddan, W. G., Pegelow, D. F., Seow, K. C., & Dempsey, J. A. (1991b). Flow limitation and regulation of functional residual capacity during exercise in a physically active aging population. *Am Rev Respir Dis, 143*(5 Pt 1), 960-967.

Johnson, B. D., Saupe, K. W., & Dempsey, J. A. (1992). Mechanical constraints on exercise hyperpnea in endurance athletes. *Journal of Applied Physiology, 73*(3), 874-886.

Johnson, M. A., Sharpe, G. R., & Brown, P. I. (2007). Inspiratory muscle training improves cycling time-trial performance and anaerobic work capacity but not critical power. *European journal of applied physiology, 101*(6), 761-770.

Jolley, C. J., Luo, Y.-M., Steier, J., Reilly, C., Seymour, J., Lunt, A., . . . Moxham, J. (2009). Neural respiratory drive in healthy subjects and in COPD. *European Respiratory Journal, 33*(2), 289-297.

Kaneko, H., Suzuki, A., & Horie, J. (2022). Effects of Cough Training and Inspiratory Muscle Training on Cough Strength in Older Adults: A Randomized Controlled Trial. *Lung,* 1-9.

Katayama, K., Goto, K., Shimizu, K., Saito, M., Ishida, K., Zhang, L., . . . Sheel, A. W. (2019). Effect of increased inspiratory muscle work on blood flow to inactive and active limbs during submaximal dynamic exercise. *Experimental physiology, 104*(2), 180-188.

Katayama, K., Iwamoto, E., Ishida, K., Koike, T., & Saito, M. (2012). Inspiratory muscle fatigue increases sympathetic vasomotor outflow and blood pressure during submaximal exercise. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 302*(10), R1167-R1175.

Kellerman, B. A., Martin, A. D., & Davenport, P. W. (2000). Inspiratory strengthening effect on resistive load detection and magnitude estimation. *Medicine and science in sports and exercise, 32*(11), 1859-1867.

Kemps, H. M., Thijssen, E. J., Schep, G., Sleutjes, B. T., De Vries, W. R., Hoogeveen, A. R., . . . Doevendans, P. A. (2008). Evaluation of two methods for continuous cardiac output assessment during exercise in chronic heart failure patients. *Journal of Applied Physiology, 105*(6), 1822-1829.

Kennedy, E., Albert, M., & Nicholson, H. (2017). The fascicular anatomy and peak force capabilities of the sternocleidomastoid muscle. *Surgical and Radiologic Anatomy, 39*(6), 629-645.

Kenyon, C., Cala, S., Yan, S., Aliverti, A., Scano, G., Duranti, R., . . . Macklem, P. T. (1997). Rib cage mechanics during quiet breathing and exercise in humans. *Journal of Applied Physiology, 83*(4), 1242-1255.

Kervio, G., Carre, F., & Ville, N. S. (2003). Reliability and intensity of the six-minute walk test in healthy elderly subjects. *Medicine and science in sports and exercise, 35*(1), 169-174.

Kikuchi, Y., Hida, W., Chonan, T., Shindoh, C., Sasaki, H., & Takishima, T. (1991). Decrease in functional residual capacity during inspiratory loading and the sensation of dyspnea. *Journal of applied physiology (Bethesda, Md.: 1985), 71*(5), 1787-1794.

Killian, K., Summers, E., Jones, N., & Campbell, E. (1992). Dyspnea and Leg Effort during Incremental Cycle Ergometry1-3. *Am Rev Respir Dis, 145*, 1339-1345.

Klas, J. V., & Dempsey, J. A. (1989). Voluntary Versus Reflex Regulation of Maximal Exercise Flow: Volume Loops1-3. *The American review of respiratory disease, 139*, 150-156.

Konno, K., & Mead, J. (1967). Measurement of the separate volume changes of rib cage and abdomen during breathing. *Journal of Applied Physiology, 22*(3), 407-422.

Koppers, R. J., Vos, P. J., Boot, C. R., & Folgering, H. T. M. (2006). Exercise performance improves in patients with COPD due to respiratory muscle endurance training. *Chest, 129*(4), 886-892.

Krumpe, P. E., Knudson, R. J., Parsons, G., & Reiser, K. (1985). The aging respiratory system. *Clinics in geriatric medicine, 1*(1), 143-175.

Kubicek, W., Karnegis, J., Patterson, R., Witsoe, D., & Mattson, R. (1966). Development and evaluation of an impedance cardiac output system. *Aerospace Medicine, 37*(12), 1208-1212.

Laghi, F., Shaikh, H. S., Morales, D., Sinderby, C., Jubran, A., & Tobin, M. J. (2014). Diaphragmatic neuromechanical coupling and mechanisms of hypercapnia during inspiratory loading. *Respiratory physiology & neurobiology, 198*, 32-41.

Langer, D., Charususin, N., Jácome, C., Hoffman, M., McConnell, A., Decramer, M., & Gosselink, R. (2015). Efficacy of a novel method for inspiratory muscle training in people with chronic obstructive pulmonary disease. *Physical therapy, 95*(9), 1264-1273.

Langer, D., Ciavaglia, C., Faisal, A., Webb, K. A., Neder, J. A., Gosselink, R., . . . O'Donnell, D. E. (2018). Inspiratory muscle training reduces diaphragm activation and dyspnea during exercise in COPD. *Journal of Applied Physiology, 125*(2), 381-392.

Laoutaris, I., Dritsas, A., Brown, M. D., Manginas, A., Alivizatos, P. A., & Cokkinos, D. V. (2004). Inspiratory muscle training using an incremental endurance test alleviates dyspnea and improves functional status in patients with chronic heart failure. *European Journal of Cardiovascular Prevention & Rehabilitation, 11*(6), 489-496.

Larson, J., & Kim, M. (1987). Ineffective breathing pattern related to respiratory muscle fatigue. *The Nursing Clinics of North America, 22*(1), 207-223.

Laveneziana, P., Albuquerque, A., Aliverti, A., Babb, T., Barreiro, E., Dres, M., . . . Guenette, J. A. (2019). ERS statement on respiratory muscle testing at rest and during exercise. *European Respiratory Journal, 53*(6).

Laveneziana, P., Webb, K. A., Ora, J., Wadell, K., & O'Donnell, D. E. (2011). Evolution of dyspnea during exercise in chronic obstructive pulmonary disease: impact of critical volume constraints. *American Journal of Respiratory and Critical Care Medicine, 184*(12), 1367-1373.

Laviolette, L., & Laveneziana, P. (2014). Dyspnoea: a multidimensional and multidisciplinary approach. *European Respiratory Journal, 43*(6), 1750-1762.

Layton, A. M., Moran, S. L., Garber, C. E., Armstrong, H. F., Basner, R. C., Thomashow, B. M., & Bartels, M. N. (2013). Optoelectronic plethysmography compared to spirometry during maximal exercise. *Respiratory physiology & neurobiology, 185*(2), 362-368.

Leddy, A. L., Crowner, B. E., & Earhart, G. M. (2011). Utility of the Mini-BESTest, BESTest, and BESTest sections for balance assessments in individuals with Parkinson disease. *Journal of neurologic physical therapy: JNPT, 35*(2), 90.

Legrand, A., Schneider, E., Gevenois, P.-A., & De Troyer, A. (2003). Respiratory effects of the scalene and sternomastoid muscles in humans. *Journal of Applied Physiology, 94*(4), 1467-1472.

Leijon, M. E., Bendtsen, P., Ståhle, A., Ekberg, K., Festin, K., & Nilsen, P. (2010). Factors associated with patients self-reported adherence to prescribed physical activity in routine primary health care. *BMC Family Practice, 11*(1), 1-9.

Leith, D. E., & Bradley, M. (1976). Ventilatory muscle strength and endurance training. *Journal of Applied Physiology, 41*(4), 508-516.

Lewthwaite, H., Benedetti, A., Stickland, M. K., Bourbeau, J., Guenette, J. A., Maltais, F., . . . Tan, W. C. (2020). Normative peak cardiopulmonary exercise test responses in Canadian adults aged≥ 40 years. *Chest, 158*(6), 2532-2545.

LoMauro, A., Gervasoni, F., Andreoli, A., & Aliverti, A. (2021). Respiratory function assessment at the time of a new respiratory virus pandemic. *Respiratory medicine, 187*, 106570.

Lötters, F., Van Tol, B., Kwakkel, G., & Gosselink, R. (2002). Effects of controlled inspiratory muscle training in patients with COPD: a meta-analysis. *European Respiratory Journal, 20*(3), 570-577.

Louvaris, Z., Spetsioti, S., Andrianopoulos, V., Chynkiamis, N., Habazettl, H., Wagner, H., . . . Vogiatzis, I. (2019). Cardiac output measurement during exercise in COPD: A comparison of dye dilution and impedance cardiography. *The clinical respiratory journal, 13*(4), 222-231.

Mador, M. J., Magalang, U. J., Rodis, A., & Kufel, T. J. (1993). Diaphragmatic fatigue after exercise in healthy human subjects. *American Journal of Respiratory and Critical Care Medicine, 148*(6), 1571-1575.

Maher, C. G., Sherrington, C., Herbert, R. D., Moseley, A. M., & Elkins, M. (2003). Reliability of the PEDro scale for rating quality of randomized controlled trials. *Physical therapy, 83*(8), 713-721.

Mahler, D. A., Fierro-Carrion, G., & Baird, J. C. (2003). Evaluation of dyspnea in the elderly. *Clinics in geriatric medicine, 19*(1), 19-33.

Manini, T. M., Everhart, J. E., Patel, K. V., Schoeller, D. A., Colbert, L. H., Visser, M., . . . Harris, T. B. (2006). Daily activity energy expenditure and mortality among older adults. *Jama, 296*(2), 171-179.

Martin, A. M., & Woods, C. B. (2012). What sustains long-term adherence to structured physical activity after a cardiac event? *Journal of Aging and Physical Activity, 20*(2), 135-147.

Martin, J., Aubier, M., & Engel, L. (1982). Effects of inspiratory loading on respiratory muscle activity during expiration. *American Review of Respiratory Disease, 125*(3), 352-358.

Massaroni, C., Carraro, E., Vianello, A., Miccinilli, S., Morrone, M., Levai, I. K., . . . Dickinson, J. W. (2017). Optoelectronic plethysmography in clinical practice and research: a review. *Respiration, 93*(5), 339-354.

Maxwell, J. C. (1864). L. on the calculation of the equilibrium and stiffness of frames. *The London, Edinburgh, and Dublin Philosophical Magazine and Journal of Science, 27*(182), 294-299.

McClaran, S., Babcock, M., Pegelow, D., Reddan, W., & Dempsey, J. (1995). Longitudinal effects of aging on lung function at rest and exercise in healthy active fit elderly adults. *Journal of Applied Physiology, 78*(5), 1957-1968.

McConnell, A. (2013). *Respiratory Muscle Training E-Book: Theory and Practice*: Elsevier Health Sciences.

McConnell, A., Caine, M., & Sharpe, G. (1997). Inspiratory muscle fatigue following running to volitional fatigue: the influence of baseline strength. *International journal of sports medicine, 18*(03), 169-173.

McConnell, A., & Romer, L. (2004). Respiratory muscle training in healthy humans: resolving the controversy. *International journal of sports medicine, 25*(04), 284-293.

McConnell, A. K., & Griffiths, L. A. (2010). Acute cardiorespiratory responses to inspiratory pressure threshold loading. *Medicine and science in sports and exercise, 42*(9), 1696-1703.

McConnell, A. K., & Lomax, M. (2006). The influence of inspiratory muscle work history and specific inspiratory muscle training upon human limb muscle fatigue. *The Journal of physiology, 577*(1), 445-457.

McConnell, A. K., & Sharpe, G. R. (2005). The effect of inspiratory muscle training upon maximum lactate steady-state and blood lactate concentration. *European journal of applied physiology, 94*(3), 277-284.

McConnelll, A. K., & Davies, C. M. (1992). A comparison of the ventilatory responses to exercise of elderly and younger humans. *Journal of Gerontology, 47*(4), B137-B141.

McNarry, M. A., Berg, R. M., Shelley, J., Hudson, J., Saynor, Z. L., Duckers, J., . . . Mackintosh, K. A. (2022). Inspiratory Muscle Training Enhances Recovery Post COVID-19: A Randomised Controlled Trial. *European Respiratory Journal*.

Medeiros, A. I. C. d., Brandão, D. C., Souza, R. J. P. d., Fuzari, H. K. B., Barros, C. E. S. R., Barbosa, J. B. N., . . . de Melo Marinho, P. É. (2019). Effects of daily inspiratory muscle training on respiratory muscle strength and chest wall regional volumes in haemodialysis patients: a randomised clinical trial. *Disability and Rehabilitation, 41*(26), 3173-3180.

Mendes, L. P. D. S., Vieira, D. S. R., Gabriel, L. S., Ribeiro-Samora, G. A., De Andrade, A. D., Brandão, D. C., . . . Parreira, V. F. (2020). Influence of posture, sex, and age on breathing pattern and chest wall motion in healthy subjects. *Brazilian Journal of Physical Therapy, 24*(3), 240-248.

Miller, M. R. (2010). *Structural and physiological age-associated changes in aging lungs.* Paper presented at the Seminars in respiratory and critical care medicine.

Mills, D. E., Johnson, M. A., Barnett, Y. A., Smith, W. H., & Sharpe, G. R. (2015). The effects of inspiratory muscle training in older adults. *Medicine & science in sports & exercise, 47*(4), 691-697.

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med, 151*(4), 264-269, w264. doi:10.7326/0003-4819-151-4-200908180-00135

Molgat-Seon, Y., Dominelli, P. B., Ramsook, A. H., Schaeffer, M. R., Molgat Sereacki, S., Foster, G. E., . . . Sheel, A. W. (2018a). The effects of age and sex on mechanical ventilatory constraint and dyspnea during exercise in healthy humans. *Journal of Applied Physiology, 124*(4), 1092-1106.

Molgat-Seon, Y., Dominelli, P. B., Ramsook, A. H., Schaeffer, M. R., Romer, L. M., Guenette, J. A., & Sheel, A. W. (2018b). Effects of age and sex on inspiratory muscle activation patterns during exercise.

Molgat-Seon, Y., Ramsook, A. H., Peters, C. M., Schaeffer, M. R., Dominelli, P. B., Romer, L. M., . . . Sheel, A. W. (2019). Manipulation of mechanical ventilatory constraint during moderate intensity exercise does not influence dyspnoea in healthy older men and women. *The Journal of physiology, 597*(5), 1383-1399.

Montemezzo, D., Fregonezi, G. A., Pereira, D. A., Britto, R. R., & Reid, W. D. (2014). Influence of inspiratory muscle weakness on inspiratory muscle training responses in chronic heart failure patients: a systematic review and meta-analysis. *Archives of physical medicine and rehabilitation, 95*(7), 1398-1407.

Moreno, A. M., Toledo-Arruda, A. C., Lima, J. S., Duarte, C. S., Villacorta, H., & Nóbrega, A. C. (2017). Inspiratory muscle training improves intercostal and forearm muscle oxygenation in patients with chronic heart failure: evidence of the origin of the respiratory metaboreflex. *Journal of Cardiac Failure, 23*(9), 672-679.

Morgan, R., Pendleton, N., Clague, J., & Horan, M. (1997). Older people's perceptions about symptoms. *British Journal of General Practice, 47*(420), 427-430.

Moxham, J., & Jolley, C. (2009). Breathlessness, fatigue and the respiratory muscles. *Clinical medicine, 9*(5), 448.

Mummery, H. J., Stolp, B. W., deL. Dear, G., Doar, P. O., Natoli, M. J., Boso, A. E., . . . Moon, R. E. (2003). Effects of age and exercise on physiological dead space during simulated dives at 2.8 ATA. *Journal of Applied Physiology, 94*(2), 507-517.

Nasis, I., Kortianou, E., Vasilopoulou, M., Spetsioti, S., Louvaris, Z., Kaltsakas, G., . . . Vogiatzis, I. (2015). Hemodynamic effects of high intensity interval training in COPD patients exhibiting exercise-induced dynamic hyperinflation. *Respiratory physiology & neurobiology, 217*, 8-16.

Navaratnarajah, A., & Jackson, S. H. (2017). The physiology of ageing. *Medicine, 45*(1), 6-10.

Neder, J. A., Andreoni, S., Lerario, M. C., & Nery, L. E. (1999). Reference values for lung function tests: II. Maximal respiratory pressures and voluntary ventilation. *Brazilian journal of medical and biological research, 32*(6), 719-727.

Nepomuceno, V., Nepomuceno, E., Regalo, S., Cerqueira, E., & Souza, R. (2014). Electromyographic study on the sternocleidomastoid and pectoralis major muscles during respiratory activity in humans. *Journal of Morphological Sciences, 31*(02), 098-102.

Nici, L. (2000). Mechanisms and measures of exercise intolerance in chronic obstructive pulmonary disease. *Clinics in chest medicine, 21*(4), 693-704.

Nickerson, B. G., & Keens, T. G. (1982). Measuring ventilatory muscle endurance in humans as sustainable inspiratory pressure. *Journal of Applied Physiology, 52*(3), 768-772.

Niewoehner, D. E., & Kleinerman, J. (1974). Morphologic basis of pulmonary resistance in the human lung and effects of aging. *Journal of Applied Physiology, 36*(4), 412-418.

O'Donnell, D., Revill, S., & Webb, K. (2001). Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 164*(5), 770-777.

O’Connor, C., Lawson, R., Waterhouse, J., & Mills, G. H. (2019). Is inspiratory muscle training (IMT) an acceptable treatment option for people with chronic obstructive pulmonary disease (COPD) who have declined pulmonary rehabilitation (PR) and can IMT enhance PR uptake? A single-group prepost feasibility study in a home-based setting. *BMJ open, 9*(8), e028507.

O’Donnell, D. E., & Webb, K. A. (1993). Exertional breathlessness in patients with chronic airflow limitation. *Am Rev Respir Dis, 148*(5), 1351-1357.

Ofir, D., Laveneziana, P., Webb, K. A., Lam, Y.-M., & O'Donnell, D. E. (2008). Sex differences in the perceived intensity of breathlessness during exercise with advancing age. *Journal of Applied Physiology, 104*(6), 1583-1593.

Ohara, D. G., Pegorari, M., Oliveira Dos Santos, N., de Fátima Ribeiro Silva, C., Monteiro, R., Matos, A., & Jamami, M. (2018). Respiratory muscle strength as a discriminator of sarcopenia in community-dwelling elderly: a cross-sectional study. *The journal of nutrition, health & aging, 22*(8), 952-958.

Park, N. (2021). Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2020. *Office for National Statistics. Available online:* *https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2020*.

Parreira, V. F., Bueno, C. J., França, D. C., Vieira, D. S., Pereira, D. R., & Britto, R. R. (2010). Breathing pattern and thoracoabdominal motion in healthy individuals: influence of age and sex. *Brazilian Journal of Physical Therapy, 14*, 411-416.

Parreira, V. F., Vieira, D. S., Myrrha, M. A., Pessoa, I. M., Lage, S. M., & Britto, R. R. (2012). Optoelectronic plethysmography: a review of the literature. *Brazilian Journal of Physical Therapy, 16*, 439-453.

Patrick, J., Bassey, E., & Fentem, P. (1983). The rising ventilatory cost of bicycle exercise in the seventh decade: a longitudinal study of nine healthy men. *Clinical Science, 65*(5), 521-526.

Pegorari, M. S., Ruas, G., & Patrizzi, L. J. (2013). Relationship between frailty and respiratory function in the community-dwelling elderly. *Brazilian Journal of Physical Therapy, 17*(1), 09-16.

Perera, S., Mody, S. H., Woodman, R. C., & Studenski, S. A. (2006). Meaningful change and responsiveness in common physical performance measures in older adults. *Journal of the American Geriatrics Society, 54*(5), 743-749.

Petrovic, M., Reiter, M., Zipko, H., Pohl, W., & Wanke, T. (2012). Effects of inspiratory muscle training on dynamic hyperinflation in patients with COPD. *International Journal of Chronic Obstructive Pulmonary Disease, 7*, 797.

Polkey, M., Green, M., & Moxham, J. (1995). Measurement of respiratory muscle strength. *Thorax, 50*(11), 1131.

Polkey, M. I., Harris, M. L., Hughes, P. D., Hamnegärd, C., Lyons, D., Green, M., & Moxham, J. (1997). The contractile properties of the elderly human diaphragm. *American Journal of Respiratory and Critical Care Medicine, 155*(5), 1560-1564.

Potter, K., & Brandfass, K. (2015). The mini-balance evaluation systems Test (mini-BESTest). *Journal of physiotherapy, 61*(4), 225.

Quanjer, P. H., Stanojevic, S., Cole, T. J., Baur, X., Hall, G. L., Culver, B. H., . . . Zheng, J. (2012). Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations. In: Eur Respiratory Soc.

Rabe, K. F., Hurd, S., Anzueto, A., Barnes, P. J., Buist, S. A., Calverley, P., . . . Van Weel, C. (2007). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *American Journal of Respiratory and Critical Care Medicine, 176*(6), 532-555.

Rahn, H., Otis, A. B., Chadwick, L. E., & Fenn, W. O. (1946). The pressure-volume diagram of the thorax and lung. *American Journal of Physiology-Legacy Content, 146*(2), 161-178.

Ramírez-Sarmiento, A., Orozco-Levi, M., Güell, R., Barreiro, E., Hernandez, N., Mota, S., . . . Gea, J. (2002). Inspiratory muscle training in patients with chronic obstructive pulmonary disease: structural adaptation and physiologic outcomes. *American Journal of Respiratory and Critical Care Medicine, 166*(11), 1491-1497.

Ramsook, A. H., Molgat-Seon, Y., Schaeffer, M. R., Wilkie, S. S., Camp, P. G., Reid, W. D., . . . Guenette, J. A. (2017). Effects of inspiratory muscle training on respiratory muscle electromyography and dyspnea during exercise in healthy men. *Journal of Applied Physiology, 122*(5), 1267-1275.

Raper, A. J., Thompson Jr, W. T., Shapiro, W., & Patterson Jr, J. L. (1966). Scalene and sternomastoid muscle function. *Journal of Applied Physiology, 21*(2), 497-502.

Ratnovsky, A., Elad, D., & Halpern, P. (2008). Mechanics of respiratory muscles. *Respiratory physiology & neurobiology, 163*(1-3), 82-89.

Rizzato, G., & Marazzini, L. (1970). Thoracoabdominal mechanics in elderly men. *Journal of Applied Physiology, 28*(4), 457-460.

Rodman, J. R., Henderson, K. S., Smith, C. A., & Dempsey, J. A. (2003). Cardiovascular effects of the respiratory muscle metaboreflexes in dogs: rest and exercise. *Journal of Applied Physiology, 95*(3), 1159-1169.

Rodrigues, A., Da Silva, M. L., Berton, D. C., Cipriano Jr, G., Pitta, F., O'Donnell, D. E., & Neder, J. A. (2017). Maximal inspiratory pressure: does the choice of reference values actually matter? *Chest, 152*(1), 32-39.

Rodrigues, G. D., Dal Lago, P., & da Silva Soares, P. P. (2021a). Inspiratory muscle training improves breathing pattern and sympatho-vagal balance but not spontaneous baroreflex sensitivity in older women. *Respiratory physiology & neurobiology, 290*, 103672.

Rodrigues, G. D., Dal Lago, P., & da Silva Soares, P. P. (2021b). Time-dependent effects of inspiratory muscle training and detraining on cardiac autonomic control in older women. *Experimental Gerontology, 150*, 111357.

Rodrigues, G. D., Gurgel, J. L., Galdino, I. d. S., da Nóbrega, A. C. L., & Soares, P. P. d. S. (2020). Inspiratory muscle training improves cerebrovascular and postural control responses during orthostatic stress in older women. *European journal of applied physiology, 120*(10), 2171-2181.

Rodrigues, G. D., Gurgel, J. L., Gonçalves, T. R., & da Silva Soares, P. P. (2018). Inspiratory muscle training improves physical performance and cardiac autonomic modulation in older women. *European journal of applied physiology, 118*(6), 1143-1152.

Rodrigues, G. D., Gurgel, J. L., Gonçalves, T. R., & da Silva Soares, P. P. (2021). Acute effects of inspiratory loading in older women: Where the breath meets the heart. *Respiratory physiology & neurobiology, 285*, 103589.

Rodrigues, I. M., Pereira, E. T., de Castro Lopes, A. L., Massaroni, C., Baroni, G., Cerveri, P., . . . Silvatti, A. P. (2021). Is age rating enough to investigate changes in breathing motion pattern associated with aging of physically active women? *Journal of Biomechanics, 125*, 110582.

Roman, M. A., Rossiter, H. B., & Casaburi, R. (2016). Exercise, ageing and the lung. *European Respiratory Journal, 48*(5), 1471-1486.

Romer, L. M., Lovering, A. T., Haverkamp, H. C., Pegelow, D. F., & Dempsey, J. A. (2006). Effect of inspiratory muscle work on peripheral fatigue of locomotor muscles in healthy humans. *The Journal of physiology, 571*(2), 425-439.

Romer, L. M., & McConnell, A. K. (2003). Specificity and reversibility of inspiratory muscle training. *Medicine and science in sports and exercise, 35*(2), 237-244.

Romer, L. M., McConnell, A. K., & Jones, D. A. (2002a). Effects of inspiratory muscle training on time-trial performance in trained cyclists. *Journal of sports sciences, 20*(7), 547-562.

Romer, L. M., McConnell, A. K., & Jones, D. A. (2002b). Effects of inspiratory muscle training upon recovery time during high intensity, repetitive sprint activity. *International journal of sports medicine, 23*(05), 353-360.

Romer, L. M., McConnell, A. K., & Jones, D. A. (2002c). Inspiratory muscle fatigue in trained cyclists: effects of inspiratory muscle training. *Medicine and science in sports and exercise, 34*(5), 785-792.

Romer, L. M., & Polkey, M. I. (2008). Exercise-induced respiratory muscle fatigue: implications for performance. *Journal of Applied Physiology, 104*(3), 879-888.

Ross, E. Z., Nowicky, A. V., & McConnell, A. K. (2007). Influence of acute inspiratory loading upon diaphragm motor-evoked potentials in healthy humans. *Journal of Applied Physiology, 102*(5), 1883-1890.

Sawilowsky, S. S. (2009). New effect size rules of thumb. *Journal of Modern Applied Statistical Methods, 8*(2), 26.

Seixas, M. B., Almeida, L. B., Trevizan, P. F., Martinez, D. G., Laterza, M. C., Vanderlei, L. C. M., & Silva, L. P. (2019). Effects of Inspiratory Muscle Training in Older Adults. *Respiratory care*.

Shahin, B., Germain, M., Kazem, A., & Annat, G. (2008). Benefits of short inspiratory muscle training on exercise capacity, dyspnea, and inspiratory fraction in COPD patients. *International Journal of Chronic Obstructive Pulmonary Disease, 3*(3), 423.

Sheel, A. W., Derchak, P. A., Morgan, B. J., Pegelow, D. F., Jacques, A. J., & Dempsey, J. A. (2001). Fatiguing inspiratory muscle work causes reflex reduction in resting leg blood flow in humans. *The Journal of physiology, 537*(1), 277-289.

Sheel, A. W., & Romer, L. M. (2012). Ventilation and respiratory mechanics. *Comprehensive Physiology, 2*(2), 1093-1142.

Shin, H.-I., Kim, D.-K., Seo, K.-M., Kang, S.-H., Lee, S.-Y., & Son, S.-H. (2017). Relation Between Respiratory Muscle Strength and Skeletal Muscle Mass and Hand Grip Strength in the Healthy Elderly. *Annals of Rehabilitation Medicine, 41*(4), 686-692.

Simões, R. P., Castello, V., Auad, M. A., Dionísio, J., & Mazzonetto, M. (2009). Prevalence of reduced respiratory muscle strength in institutionalized elderly people. *Sao Paulo Medical Journal, 127*(2), 78-83.

Smart, N. A., Giallauria, F., & Dieberg, G. (2013). Efficacy of inspiratory muscle training in chronic heart failure patients: a systematic review and meta-analysis. *International journal of cardiology, 167*(4), 1502-1507.

Smith, J. R., Alexander, A. M., Hammer, S. M., Didier, K. D., Kurti, S. P., Broxterman, R. M., . . . Harms, C. A. (2017a). Cardiovascular consequences of the inspiratory muscle metaboreflex: effects of age and sex. *American Journal of Physiology-Heart and Circulatory Physiology, 312*(5), H1013-H1020.

Smith, J. R., Broxterman, R. M., Hammer, S. M., Alexander, A. M., Didier, K. D., Kurti, S. P., . . . Harms, C. A. (2016). Sex differences in the cardiovascular consequences of the inspiratory muscle metaboreflex. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 311*(3), R574-R581.

Smith, J. R., Cross, T. J., Van Iterson, E. H., Johnson, B. D., & Olson, T. P. (2018). Resistive and elastic work of breathing in older and younger adults during exercise. *Journal of Applied Physiology, 125*(1), 190-197.

Smith, J. R., Hageman, K. S., Harms, C. A., Poole, D. C., & Musch, T. I. (2019). Intercostal muscle blood flow is elevated in old rats during submaximal exercise. *Respiratory physiology & neurobiology, 263*, 26-30.

Smith, J. R., Kurti, S. P., Meskimen, K., & Harms, C. A. (2017b). Expiratory flow limitation and operating lung volumes during exercise in older and younger adults. *Respiratory physiology & neurobiology, 240*, 26-31.

Smith, K., Cook, D., Guyatt, G. H., Madhavan, J., & Oxman, A. D. (1992). Respiratory Muscle Training in Chronic Airflow Limitation: A Meta-Analysis1-3. *Am Rev Respir Dis, 145*, 533-539.

Souza, H., Rocha, T., Pessoa, M., Rattes, C., Brandão, D., Fregonezi, G., . . . Dornelas, A. (2014). Effects of inspiratory muscle training in elderly women on respiratory muscle strength, diaphragm thickness and mobility. *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 69*(12), 1545-1553.

Spengler, C. M., Roos, M., Laube, S. M., & Boutellier, U. (1999). Decreased exercise blood lactate concentrations after respiratory endurance training in humans. *European journal of applied physiology and occupational physiology, 79*(4), 299-305.

St Croix, C. M., Morgan, B. J., Wetter, T. J., & Dempsey, J. A. (2000). Fatiguing inspiratory muscle work causes reflex sympathetic activation in humans. *The Journal of physiology, 529*(2), 493-504.

Tak, E. C., Van Uffelen, J., Paw, M. C. A., van Mechelen, W., & Hopman-Rock, M. (2012). Adherence to exercise programs and determinants of maintenance in older adults with mild cognitive impairment. *Journal of aging and physical activity, 20*(1), 32-46.

Tan, K., Lai, F., & Hwang, N. (2006). Measurement of cardiac output using Physio Flow with different positions of electrode placement. *Singapore medical journal, 47*(11), 967-970.

Taylor, B. J., & Johnson, B. D. (2010). *The pulmonary circulation and exercise responses in the elderly.* Paper presented at the Seminars in respiratory and critical care medicine.

Tessier, J., Nejjari, C., Letenneur, L., Filleul, L., Marty, M., Gateau, P. B., & Dartigues, J. (2001). Dyspnea and 8-year mortality among elderly men and women: the PAQUID cohort study. *European journal of epidemiology, 17*(3), 223-229.

Tolep, K., Higgins, N., Muza, S., Criner, G., & Kelsen, S. G. (1995). Comparison of diaphragm strength between healthy adult elderly and young men. *American Journal of Respiratory and Critical Care Medicine, 152*(2), 677-682.

Tonelli, A. R., Alnuaimat, H., Li, N., Carrie, R., & Mubarak, K. K. (2011). Value of impedance cardiography in patients studied for pulmonary hypertension. *Lung, 189*(5), 369-375.

Tong, A., Sainsbury, P., & Craig, J. (2007). Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International journal for quality in health care, 19*(6), 349-357.

Troosters, T., Gosselink, R., & Decramer, M. (1999). Six minute walking distance in healthy elderly subjects. *European Respiratory Journal, 14*(2), 270-274.

Tsang, C. S., Liao, L.-R., Chung, R. C., & Pang, M. Y. (2013). Psychometric properties of the Mini-Balance Evaluation Systems Test (Mini-BESTest) in community-dwelling individuals with chronic stroke. *Physical therapy, 93*(8), 1102-1115.

Turner, J. M., Mead, J., & Wohl, M. E. (1968). Elasticity of human lungs in relation to age. *Journal of Applied Physiology, 25*(6), 664-671.

Turner, L. A., Mickleborough, T. D., McConnell, A. K., Stager, J. M., & Tecklenburg-Lung, S. (2011). Effect of Inspiratory Muscle Training on Exercise Tolerance in Asthmatic Individuals. *Medicine & Science in Sports & exercise: Official Journal of the American College of Sports Medicine, 43*(11), 2031-2038.

Turner, L. A., Tecklenburg-Lund, S. L., Chapman, R. F., Stager, J. M., Wilhite, D. P., & Mickleborough, T. D. (2012). Inspiratory muscle training lowers the oxygen cost of voluntary hyperpnea. *Journal of Applied Physiology, 112*(1), 127-134.

Tzelepis, G. E., Vega, D. L., Cohen, M. E., Fulambarker, A. M., Patel, K., & McCool, F. (1994). Pressure-flow specificity of inspiratory muscle training. *Journal of Applied Physiology, 77*(2), 795-801.

Van der Palen, J., Rea, T., Manolio, T., Lumley, T., Newman, A., Tracy, R., . . . Psaty, B. (2004). Respiratory muscle strength and the risk of incident cardiovascular events. *Thorax, 59*(12), 1063-1067.

Van Hollebeke, M., Gosselink, R., & Langer, D. (2020). Training specificity of inspiratory muscle training methods: a randomized trial. *Frontiers in Physiology*, 1551.

Verbeken, E. K., Cauberghs, M., Mertens, I., Clement, J., Lauweryns, J. M., & Van de Woestijne, K. P. (1992). The senile lung: comparison with normal and emphysematous lungs 1. Structural aspects. *Chest, 101*(3), 793-799.

Verschakelen, J. A., & Demedts, M. G. (1995). Normal thoracoabdominal motions. Influence of sex, age, posture, and breath size. *American Journal of Respiratory and Critical Care Medicine, 151*(2), 399-405.

Vieira, D. S., Hoffman, M., Pereira, D. A., Britto, R. R., & Parreira, V. F. (2013). Optoelectronic plethysmography: intra-rater and inter-rater reliability in healthy subjects. *Respiratory physiology & neurobiology, 189*(3), 473-476.

Vogiatzis, I., Aliverti, A., Golemati, S., Georgiadou, O., LoMauro, A., Kosmas, E., . . . Roussos, C. (2005). Respiratory kinematics by optoelectronic plethysmography during exercise in men and women. *European journal of applied physiology, 93*(5), 581-587.

Vogiatzis, I., Athanasopoulos, D., Habazettl, H., Aliverti, A., Louvaris, Z., Cherouveim, E., . . . Zakynthinos, S. (2010). Intercostal muscle blood flow limitation during exercise in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine, 182*(9), 1105-1113.

Vogiatzis, I., & Zakynthinos, S. (2012). Factors limiting exercise tolerance in chronic lung diseases. *Comprehensive Physiology, 2*(3), 1779-1817.

Volianitis, S., McConnell, A. K., Koutedakis, Y., McNaughton, L. R., Backx, K., & Jones, D. A. (2001). Inspiratory muscle training improves rowing performance.

Wagner, P. D., Laravuso, R. B., Uhi, R. R., & West, J. B. (1974). Continuous Distributions of Ventilation-Perfusion Ratios in Normal Subjects Breathing Air and 100% O2. *Journal of Clinical Investigation, 54*(1), 54.

Wanke, T., Formanek, D., Lahrmann, H., Brath, H., Wild, M., Wagner, C., & Zwick, H. (1994). Effects of combined inspiratory muscle and cycle ergometer training on exercise performance in patients with COPD. *European Respiratory Journal, 7*(12), 2205-2211.

Ware Jr, J. E., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36): I. Conceptual framework and item selection. *Medical care*, 473-483.

Watsford, M., & Murphy, A. (2008). The effects of respiratory-muscle training on exercise in older women. *Journal of aging and physical activity, 16*(3), 245-260.

Watsford, M. L., Murphy, A. J., & Pine, M. J. (2007). The effects of ageing on respiratory muscle function and performance in older adults. *Journal of Science and Medicine in Sport, 10*(1), 36-44.

Weiner, P., Magadle, R., Beckerman, M., Weiner, M., & Berar-Yanay, N. (2003). Comparison of specific expiratory, inspiratory, and combined muscle training programs in COPD. *Chest, 124*(4), 1357-1364.

Weiner, P., Magadle, R., Berar-Yanay, N., & Pelled, B. (1999). The effect of specific inspiratory muscle training on the sensation of dyspnea and exercise tolerance in patients with congestive heart failure. *Clinical cardiology, 22*(11), 727-732.

Welch, J. F., Kipp, S., & Sheel, A. W. (2019). Respiratory muscles during exercise: mechanics, energetics, and fatigue. *Current Opinion in Physiology, 10*, 102-109.

West, J. B. (2012). *Respiratory physiology: the essentials*: Lippincott Williams & Wilkins.

Wetter, T. J., Harms, C. A., Nelson, W. B., Pegelow, D. F., & Dempsey, J. A. (1999). Influence of respiratory muscle work onV˙ o 2 and leg blood flow during submaximal exercise. *Journal of Applied Physiology, 87*(2), 643-651.

Wilkie, S. S., Guenette, J. A., Dominelli, P. B., & Sheel, A. W. (2012). Effects of an aging pulmonary system on expiratory flow limitation and dyspnoea during exercise in healthy women. *European journal of applied physiology, 112*(6), 2195-2204.

Wilson, R. C., & Jones, P. (1989). A comparison of the visual analogue scale and modified Borg scale for the measurement of dyspnoea during exercise. *Clinical Science, 76*(3), 277-282.

Wilson, S., Cooke, N., Edwards, R., & Spiro, S. (1984). Predicted normal values for maximal respiratory pressures in caucasian adults and children. *Thorax, 39*(7), 535-538.

Windisch, W., Hennings, E., Sorichter, S., Hamm, H., & Criee, C. (2004). Peak or plateau maximal inspiratory mouth pressure: which is best? *European Respiratory Journal, 23*(5), 708-713.

Witt, J. D., Guenette, J. A., Rupert, J. L., McKenzie, D. C., & Sheel, A. W. (2007). Inspiratory muscle training attenuates the human respiratory muscle metaboreflex. *The Journal of physiology, 584*(3), 1019-1028.

Wu, J., Kuang, L., & Fu, L. (2018). Effects of inspiratory muscle training in chronic heart failure patients: a systematic review and meta-analysis. *Congenital heart disease, 13*(2), 194-202.

Yingyongyudha, A., Saengsirisuwan, V., Panichaporn, W., & Boonsinsukh, R. (2016). The Mini-Balance Evaluation Systems Test (Mini-BESTest) demonstrates higher accuracy in identifying older adult participants with history of falls than do the BESTest, Berg Balance Scale, or Timed Up and Go Test. *Journal of geriatric physical therapy, 39*(2), 64-70.

Zhang, J., Schaeffer, M. R., Mitchell, R. A., Boyle, K. G., Hutchinson, O. N., Puyat, J. H., & Guenette, J. A. (2020). A multidimensional assessment of dyspnoea in healthy adults during exercise. *European journal of applied physiology, 120*(11), 2533-2545.

Appendices

Appendix 1 – Participant information sheet (Chapter 5)

Title: study: Acute effects of the POWERbreathe inspiratory muscle trainer on chest wall volumes in young and older individuals.

<u>Participant Information Sheet</u>

<u>What is the purpose of this study?</u>
Inspiratory muscle training devices has been proven to improve inspiratory muscle strength, endurance and exercise performance in both healthy and diseased populations. By overloading these muscles with various resistances, the device will increase the effort of breathing and activation of respiratory muscles such as the diaphragm and rib cage muscles.
The aim of this study is to evaluate different levels of inspiratory resistances using the POWERbreathe KH1 inspiratory muscle trainer (Figure 1) on chest wall volumes in healthy young and old adults. The pattern of this muscle activation during different inspiratory resistances between healthy young and old adults remains unclear.

<u>Why have I been chosen?</u>
You have been chosen because you are a either a healthy adult aged between 18–30 or 60–75 with no long-term conditions such as chronic obstructive pulmonary disease or chronic heart failure and are not a current smoker or have asthma.

<u>Do I have to take part?</u>
You do not have to take part. If you wish to take part you will be asked to sign a consent form. You may withdraw from the study at any time, and do not have to give a reason for doing so.

<u>What happens if I take part in this study?</u>
If you chose to take part in this study you will be required to visit the biomechanics gait laboratory at Sport Central, Northumbria University on one occasion. The visit will last approximately two hours and involve your participation in four trials (one quiet breathing and three with inspiratory resistance).

You will initially be required to perform a maximal inspiratory pressure manoeuvre through the inspiratory muscle trainer in order to calculate the individualised resistances for the inspiratory loaded trials (30, 50 and 70% of maximum value). This manoeuvre will involve breathing out fully then taking a forceful breath in against a resistance as hard you can using a Powerbreathe device (Figure 1) inspiratory muscle trainer. You will then be required to perform spirometry tests to check for normal lung function before removing any upper body clothing (women can wear sports bra/bra) so we can attach 89 reflective markers in order to be recorded by cameras in the laboratory (Figure 2).

The order of the three inspiratory loaded trials will be randomised and therefore be different for each individual. Each trial will involve you to sit on a chair so that you are in full view of all the cameras. During the quiet breathing trials, you will simply be instructed to breath normally for 3 minutes. You will then be required to breathe through the inspiratory muscle trainer at either 30, 50 or 70% of your maximal value) for 1 minute after a period of normal breathing before you have time to recover. A pick-up line will be attached to the inspiratory muscle training device's mouthpiece in order to measure oxygen and carbon dioxide levels. You will then be required to breathe through the inspiratory muscle trainer at a different resistance for another minute. This process will be repeated once more for the final inspiratory resistance.

You may be required to repeat these inspiratory loaded trials whilst breathing at a slower rate in order for the researchers to determine whether the speed of breathing affects the variables recorded. If there are any technical difficulties which lead to the inability to collect data, you may be asked to return to the laboratory on a separate occasion, however, this is an unlikely circumstance.

What are the potential risks of taking part?

You may feel slightly dizzy or out of breath whilst breathing through the inspiratory muscle trainer. If you are constantly feeling dizzy or lightheaded you should signal to the researchers and the trial will be terminated. Furthermore, the researchers will be nearby to prevent the risk of fainting or falling off the chair.

What are the advantages of taking part?

You will have an opportunity to experience state of the art equipment and technology within the laboratory, and, although the use of the inspiratory muscle trainer may not directly benefit your life (due to already having healthy inspiratory muscles), you will be a part of a research project which may determine mechanisms behind the effectiveness of this device.

Will my personal information be confidential?

The data you provide will be treated in accordance with the General Data Protection Regulations (GDPR). Your name and date of birth will be kept confidential and will only be available to the research team.

Where will my results be stored?

Your results obtained from this study will be securely stored on a password protected computer within the laboratory and will only be viewed by members of the research team. If you wish to view your results at any time, please contact the researcher using the details shown at the bottom of this sheet.

What will happen to the results following this study?

The results obtained from this study will hopefully be published in scientific journals, discussed at meetings and presented at conferences, enabling the research team to pass on findings to other healthcare professionals and researchers.

Who is Organizing and Funding the Study?

The study will be organised and funded by Northumbria University.

COVID-19 safety measures

There will be a number of safety measures in place to reduce the risk of exposure to COVID-19 during this testing visit. When attending testing we would require that you come already dressed in appropriate gym clothing or comfortable clothing to avoid having to get changed on site. There is a one-way system to the laboratory in which JM will meet all participants outside of sports central and take them to the laboratory for testing. Participants will be required to use the hand sanitiser when entering and leaving sports central. During the testing there will be three researchers present, and only one of these will be required to be in close contact to put the markers on your body. All researchers will undergo weekly lateral flow COVID-19 testing.

Due to having to attach 89 markers on the body we cannot maintain a 2 m distance during all of the testing. Where close contact is required the participant will be provided with a Type IIR Fluid Repellent face mask to wear. The researcher will also wear appropriate PPE equipment such as an Apron, gloves, type IIR mask and visor (Figure 3). We aim to keep the close contact to a minimum time period to avoid prolonged contact. Once all of the markers are in place and calibrated the researcher can then maintain a 2 m social distance. Once testing is complete the researcher will sterilise all mouthpieces and disinfect equipment and worksurfaces.
We are doing everything we can to make our campus as covid-secure as possible and to manage your attendance safely. To do this, we will provide you with the following:

1. COVID-19 measures - what to expect on campus
2. Participant COVID-19 Exposure Declaration
3. Vulnerable to COVID-19 Self-Assessment

The first document provides general guidance on COVID-19 safety measures to expect on campus as well as your role in supporting the measures we have put in place.

To support known or potentially vulnerable groups, the “Vulnerable to COVID-19 self-assessment” will help you self-identify if you may be at higher risk to COVID-19. Please complete the self-assessment and contact the researcher if your risk level scores higher than 3.1 as this allows researchers to put in place additional safety precautions.

We have also introduced a multi-step screening process to help prevent the spread of COVID-19 and reduce the risk of exposure to our staff and research participants, we ask that complete these declaration and return electronically signed. This declaration form will be used for the duration of the study and a researcher will contact you 24 hours before each attendance on campus to confirm that your COVID-19 circumstances have not changed. If your circumstances do change prior to this phone call, for example if you start to feel unwell or have been in contact with a confirmed case of COVID-19, or if they change in the 14 days after your visit, please inform the researcher.

Who has reviewed this study?

Before the study can begin, permission will be obtained from Northumbria University. The study and its protocol have received full ethical approval from the Chair of the Faculty of Health and Life Sciences Ethics Committee. If you require confirmation of this, please contact the Chair of the Faculty of Health and Life Sciences Ethics Committee (Claire Thornton claire.thronton@northumbria.ac.uk) and stating the full title and principal investigator of the study.

What if I need more information on this study?

If you encounter any problems, or simply wish to acquire more information about this study, please contact the researchers using the contact details found below.

Figure 1. The inspiratory muscle trainer you will be required to breathe through.

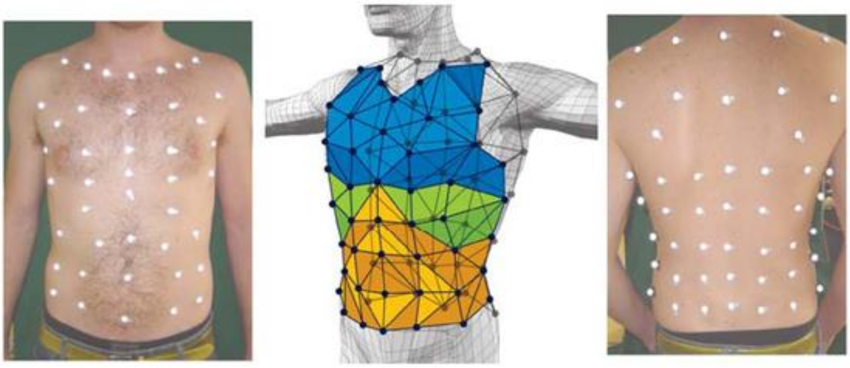


Figure 2. The 89 markers that will be attached to measure chest wall volume responses.

Unsuspected COVID-19
PPE General Area

Eye Protection / Visor *

*self assessment of risk for eye protection session or single use

Fluid Resistant Surgical Mask*

*self assessment of risk for mask session or single use

Hand hygiene

Wash your hands with non-antimicrobial liquid soap and water if:

- visibly soiled or dirty;
- caring for a patient with a suspected or known gastro-intestinal infection e.g. norovirus or a spore forming organism i.e. C.difficile
- Immediately after removal of PPE.

In all other circumstances alcohol based hand rub can be used as an alternative to hand washing with liquid soap and water.

Gloves must be:

- worn when exposure to blood and/or other body fluids is anticipated/likely e.g. toileting or taking blood;
- changed immediately after each patient and/or following completion of a procedure or task;
- changed if a perforation or puncture is suspected;
- appropriate for use, fit for purpose and well-fitting.

Aprons must be:

- worn to protect uniform or clothes when contamination is anticipated/likely e.g. when undertaking direct care e.g. assisted wash or aseptic/clean task
- changed between patients and/or following completion of a procedure or task.

Remember to perform hand hygiene following removal/disposal of PPE.

Please refer to the full UK COVID-19 guidance for Infection Prevention and Control on the HPS COVID-19 web page

April 2020 poster 1 Green precautions general area V1

Figure 3. Personal protective equipment used.

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Appendix 2 – Participant information sheet (Chapter 6)

Northumbria University
NEWCASTLE

Title: Effects of inspiratory muscle training on respiratory kinematics and exercise capacity in older adults.

Participant Information Sheet

What is the purpose of this study?

Inspiratory muscle training devices have been proven to improve inspiratory muscle strength, endurance and exercise performance in both healthy and diseased populations, however, there is little known about the effects of this device in healthy older adults.

The aim of this study is to determine the effects of an 8-week inspiratory muscle training programme on exercise capacity, chest wall volume and heart rate responses, along with balance, and physical activity levels.

Why have I been chosen?

You have been chosen because you are an adult between 60 and 75 years old with no long-term conditions, such as chronic obstructive pulmonary disease or chronic heart failure and are not a current smoker or have asthma.

Do I have to take part?

You do not have to take part. If you wish to take part, you will be asked to sign a consent form. You may withdraw from the study at any time, and do not have to give a reason for doing so.

What happens if I take part in this study?

If you chose to take part in this study you will be required to visit the biomechanics gait laboratory at Sport Central, Northumbria University on three separate occasions. Within this study you will be randomly assigned to a training group (strength or endurance).

One week prior to your first visit, you will be required to wear an activity monitor around your waist for one week as you go about your daily routines to determine your physical activity levels. If you are interested in participating in this study we will arrange a time for this activity monitor to be picked up/dropped off.

The first visit will be to assess study eligibility (via health screening questionnaires) and measure baseline respiratory muscle strength, lung function and exercise capacity. The respiratory muscle strength and lung function tests will require you to breathe forcefully through a mouthpiece both with and without added resistance. If there are any abnormalities found during your lung function assessment, the researcher will talk you through this and contact your GP. You will then be required to perform a walk test which will involve you walking as many 30 m shuttles as possible in six minutes.

After an adequate rest you will be required to perform balance tests and fill out a quality of life questionnaire. The balance tests will involve a battery of short tests lasting, overall, around 15 minutes. You will then be required to perform a cycling exercise test. Before the exercise test you will be asked to remove any upper body clothing (women can wear a sports bra) in order for 89 reflective markers to be attached, which record chest wall volumes, and adhesive pads that measure heart activity. This exercise will be performed on a stationary bike at a fixed intensity (calculated as 75% predicted maximum work rate), and you will be required to pedal at a given speed until exhaustion.

Finally, you will be given and instructed on how to use the inspiratory muscle training device and training diaries, before completing one training bout. This visit will last around 3 hours.
You will then return home and be expected to train with the inspiratory muscle training device twice daily, 7 days a week, for 8 weeks and fill out the training diary after each session. Training sessions will involve breathing in against resistance for 30 breaths in order to train your respiratory muscles. Each home-based training session will last around 5 minutes.
The third visit to the lab will take place after 4 weeks of training at the mid-point of the programme and will involve reassessing your respiratory muscle strength and to perform another training bout. This should last around half an hour.

After another 4 weeks of training at home, you will be required to return to the lab one final time to repeat the cycle exercise, walk tests, balance, and quality of life test from previous visits. This will last around 3 hours. You will also be administered with the activity monitor again to wear for one week to see if the training programme has changed your physical activity levels.

You may also be invited to take part in an interview where you will be asked open-ended questions regarding their perceptions, experiences and acceptance of the inspiratory muscle training programme.

What are the potential risks of taking part?

During the exercise tests, it is likely that your will feel discomfort in your legs and perhaps your breathing. Although extremely rare (around 0.008%), there is risk of a serious adverse event during the exercise test (eg. heart attack/death), but you will be monitored closely (via heart rate, oxygen levels, and self-reported symptoms), and exercise tests will be terminated prematurely if required. There will also always be a member of staff first aid trained in the vicinity. You may experience muscle soreness in your legs after the test, but this will be mild and pass after a few days.
During the inspiratory muscle training programme at home you may feel slightly dizzy or out of breath whilst breathing through the device. The researchers will coach you through the correct technique of using the device during the first visits to the lab, however, if you are constantly feeling dizzy or lightheaded you should contact the researchers for further advice.

What are the advantages of taking part?

You will have an opportunity to experience state of the art equipment and technology within the lab. The inspiratory muscle training programme may result in an increased strength or endurance of the respiratory muscles which could translate into improved exercise capacity, however, we cannot guarantee this.

Will my personal information be confidential?

The data you provide will be treated in accordance with the General Data Protection Regulations (GDPR). Your name and date of birth will be kept confidential and will only be available to the research team.

Where will my results be stored?

Your results obtained from this study will be securely stored on a password protected computer within the lab and will only be viewed by members of the research team. If you wish to view your results at any time, please contact the researcher using the details shown at the bottom of this sheet.

What will happen to the results following this study?

The results obtained from this study will hopefully be published in scientific journals, discussed at meetings and presented at conferences, enabling the research team to pass on findings to other healthcare professionals and researchers.

Who is Organizing and Funding the Study?

The study will be organised and funded by Northumbria University.

COVID-19 safety measures

There will be a number of safety measures in place to reduce the risk of exposure to COVID-19 during this testing visit. When attending testing we would require that you come already dressed in appropriate gym clothing or comfortable clothing to avoid having to get changed on site. There is a one-way system to the laboratory in which JM will meet all participants outside of sports central and take them to the laboratory for testing. Participants will be required to use the hand sanitiser when entering and leaving sports central. During the testing there will be three researchers present, and only one of these will be required to be in close contact to put the markers on your body. All researchers will undergo weekly lateral flow COVID-19 testing.

Due to having to attach 89 markers on the body we cannot maintain a 2 m distance during all of the testing. Where close contact is required the participant will be provided with a Type IIR Fluid Repellent face mask to wear. The researcher will also wear appropriate PPE equipment such as an Apron, gloves, type IIR mask and visor (Figure 1). We aim to keep the close contact to a minimum time period to avoid prolonged contact. Once all of the markers are in place and calibrated the researcher can then maintain a 2 m social distance. Once testing is complete the researcher will sterilise all mouthpieces and disinfect equipment and worksurfaces.
We are doing everything we can to make our campus as covid-secure as possible and to manage your attendance safely. To do this, we will provide you with the following:

1. COVID-19 measures - what to expect on campus
2. Participant COVID-19 Exposure Declaration
3. Vulnerable to COVID-19 Self-Assessment

The first document provides general guidance on COVID-19 safety measures to expect on campus as well as your role in supporting the measures we have put in place.

To support known or potentially vulnerable groups, the “Vulnerable to COVID-19 self-assessment” will help you self-identify if you may be at higher risk to COVID-19. Please complete the self-assessment and contact the researcher if your risk level scores higher than 3.1 as this allows researchers to put in place additional safety precautions.

We have also introduced a multi-step screening process to help prevent the spread of COVID-19 and reduce the risk of exposure to our staff and research participants, we ask that complete these declaration and return electronically signed. This declaration form will be used for the duration of the study and a researcher will contact you 24 hours before each attendance on campus to confirm that your COVID-19 circumstances have not changed. If your circumstances do change prior to this phone call, for example if you start to feel unwell or have been in contact with a confirmed case of COVID-19, or if they change in the 14 days after your visit, please inform the researcher.

Who has reviewed this study?

Before the study can begin, permission will be obtained from Northumbria University. The study and its protocol have received full ethical approval from the Chair of the Faculty of Health and Life Sciences Ethics Committee. If you require confirmation of this, please contact the Chair of the Faculty of Health and Life Sciences Ethics Committee (Claire Thornton claire.thornton@northumbria.ac.uk) and stating the full title and principal investigator of the study.

What if I need more information on this study?

If you encounter any problems, or simply wish to acquire more information about this study, please contact the researchers using the contact details found below.

Contact details:
James Manifield
PhD student
Department of Sport, Exercise and Rehabilitation
Faculty of Health and Life Sciences
Northumbria University
Email: james.manifield@northumbria.ac.uk

Dr. Gill Barry
Senior Lecturer in Biomechanics
Department of Sport, Exercise and Rehabilitation
Faculty of Health and Life Sciences
Northumbria University
Email: gill.barry@northumbria.ac.uk

Figure 1. Personal protective equipment used.

Appendix 3 – Informed consent sheet (Chapter 5)

Informed consent

Title: Acute effects of the POWERbreathe inspiratory muscle trainer on chest wall volumes in young and older individuals.

Name of researcher: James Manifield

Please tick boxes

I have read the participant information sheet for this study	
I have had the opportunity to consider this information and ask questions which have been answered to my satisfaction	
I understand that my participation in this study is voluntary and I can withdraw at any time without having to give a reason for doing so	
I understand that the information obtained from this study will be used in future reports and presentations by the research team	
I understand that my personal information will be kept confidential and will not appear in these future reports and presentations	
I agree to take part in the above study	

Please contact the ADRI if you wish to make a complaint about the conduct of this study

________________________ ______________ ________________________

Participant name (print) **Date** **Participant signature**

________________________ _____________ _________________________

Researcher name (print) **Date** **Researcher signature**

Appendix 4 – Informed consent sheet (Chapter 6)

Informed consent

Title: Effects of inspiratory muscle training on respiratory kinematics and exercise capacity in older adults.

Name of researcher: James Manifield

Please tick boxes

I have read the participant information sheet for this study	☐
I have had the opportunity to consider this information and ask questions which have been answered to my satisfaction	☐
I understand that my participation in this study is voluntary and I can withdraw at any time without having to give a reason for doing so	☐
I understand that the information obtained from this study will be used in future reports and presentations by the research team	☐
I understand that my personal information will be kept confidential and will not appear in these future reports and presentations	☐
I agree to take part in the above study	☐

Please contact the Chair of the Faculty of Health and Life Sciences Ethics Committee (Claire Thornton claire.thornton@northumbria.ac.uk) and state the full title and principal investigator of the study if you wish to make a complaint about the conduct of this study.

____________________ __________________ ________________________

Participant name (print) **Date** **Participant signature**

____________________ __________________ ________________________

Researcher name (print) **Date** **Researcher signature**

Appendix 5 – Informed consent sheet (Chapter 7)

Informed consent - Interviews

Title: Effects of inspiratory muscle training on respiratory kinematics and exercise capacity in older adults.

Name of researcher: James Manifield

Please tick boxes

I have read the participant information sheet for this study	
I have had the opportunity to consider this information and ask questions which have been answered to my satisfaction	
I understand that my participation in this study is voluntary and I can withdraw at any time without having to give a reason for doing so	
I understand that the information obtained from this study will be used in future reports and presentations by the research team	
I understand that my personal information will be kept confidential and will not appear in these future reports and presentations	
I understand that I have the right to decline to answer any questions.	
I understand that the interview will be audio and video recorded, and that these files will be kept on secure, password protected computers only accessible by the research team.	
I understand that I may be contacted in the future for follow-up interviews	
I agree to take part in the above study	

Please contact the Chair of the Faculty of Health and Life Sciences Ethics Committee (Claire Thornton claire.thornton@northumbria.ac.uk) and state the full title and principal investigator of the study if you wish to make a complaint about the conduct of this study.

Participant name (print) **Date** **Participant signature**

Researcher name (print) **Date** **Researcher signature**

Appendix 6 – Training diary information for strength (IMT) and control (SHAM-IMT; endurance; chapter 6)

TRAINING DIARY – STRENGTH GROUP

Participant ID:

Important information:

- Aim to perform 30 continuous breaths twice a day (morning and evening).
- Write down how many breaths you perform in each session under ‘duration’.
- Breathe in against the load with maximum effort (as hard/fast as you can) AND as far in as possible.
- Make sure you are getting sufficient air in with each breath, if you are struggling to get air in then the load is too high.
- Breathe out normally but empty your lungs after each breath.
- If you feel dizzy remove the mouthpiece and rest for a minute before continuing.
- Write down the ‘level’ (where the arrow is pointing on the device) for each session.
- You should aim to train at an intensity of 4–6 on the rating of breathing discomfort scale below, typically reaching failure (inability to achieve a satisfying breath) around 30 breaths – write down your rating after each training session under ‘effort’.
- If you reach failure before 30 breaths during a session, please write down how many breaths you completed in the ‘duration’ box.
- If you reach 30 breaths with ease (rating <4) you may increase the load by a one-quarter turn but make sure to write down if you have done this in the ‘level’ box (e.g., if you find 30 breaths at level 2 is too easy, turn the device clockwise by one-quarter and write down 2.25 as the level. If after a few

more sessions this level is too easy, turn another one-quarter and write 2.5 as the level etc.).

- If for any reason you miss a training session, please make a note of this next to ‘notes’ with the day/session and reason.

TRAINING DIARY – ENDURANCE GROUP

Participant ID:

Important information:

- Perform 30 continuous breaths twice a day (morning and evening). If for any reason you do not reach 30 breaths, write down how many breaths you perform in each session under ‘duration’.
- Breathe in against the load with maximum effort (as hard/fast as you can) AND as far in as possible.
- Breathe out normally but empty your lungs after each breath.
- If you feel dizzy remove the mouthpiece and rest for a minute before continuing.
- Please do not adjust the intensity (where the arrow is pointing on the device) over the course of the training programme – the ‘level’ should be consistent throughout.
- Write down your rating of breathing discomfort using the scale below after each training session under ‘effort’.
- If for any reason you miss a training session, please make a note of this next to ‘notes’ with the day/session and reason.

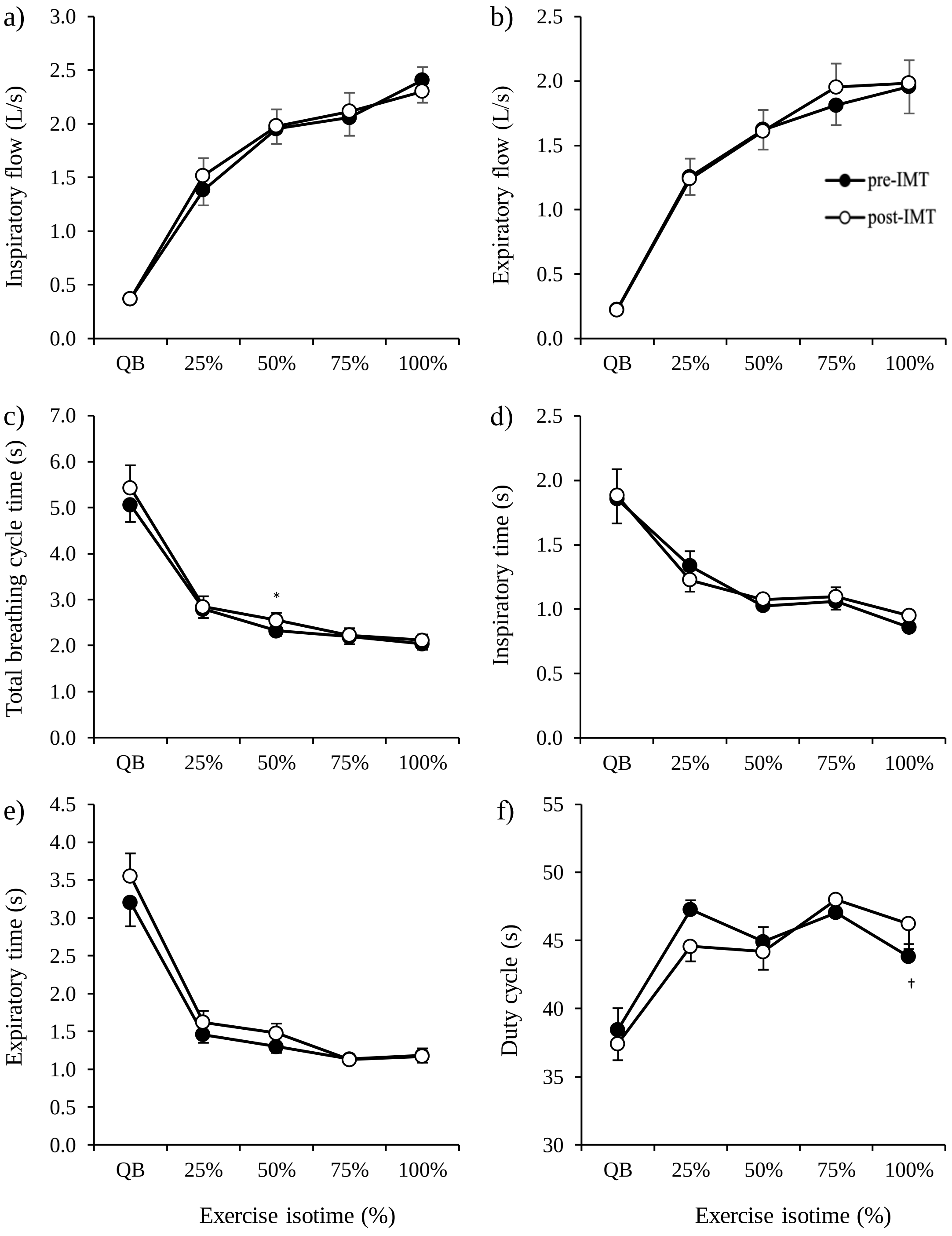
Appendix 7 – Example of training diary week

Week number	**Monday**			**Tuesday**			**Wednesday**			**Thursday**			**Friday**			**Saturday**			**Sunday**		
	Level	**Duration**	**Effort**	**Level**	**Duration**	**Effort**	**Level**	**Duration**	**Effort**	**Level**	**Duration**	**Effort**	**Level**	**Duration**	**Effort**	**Level**	**Duration**	**Effort**	**Level**	**Duration**	**Effort**
Morning																					
Evening																					

Notes:

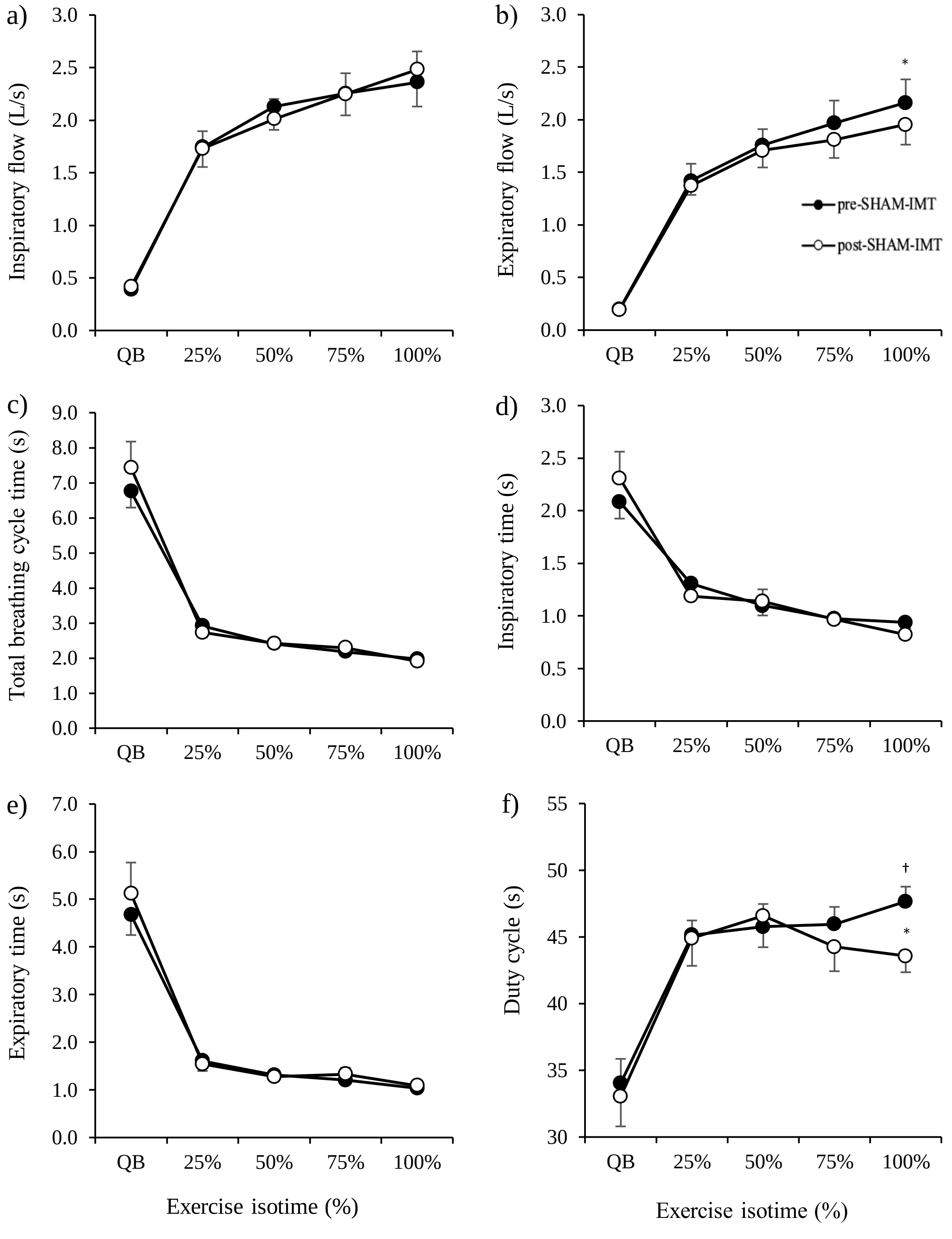
Appendix 8 – Baseline and post-intervention breathing pattern variables (chapter 6)

INTERVENTION GROUP



Changes in inspiratory flow (*a*), expiratory flow (*b*), total time of breathing cycle (*c*), inspiratory time (*d*), expiratory time (*e*), and duty cycle (*f*) within the IMT group at pre- (*closed symbols*) and post-intervention (*open symbols*) during quiet breathing (QB) and exercise isotime (25%, 50%, 75%, and 100%) in the IMT group. *denote significant difference from pre-intervention; † significant difference between intervention groups.

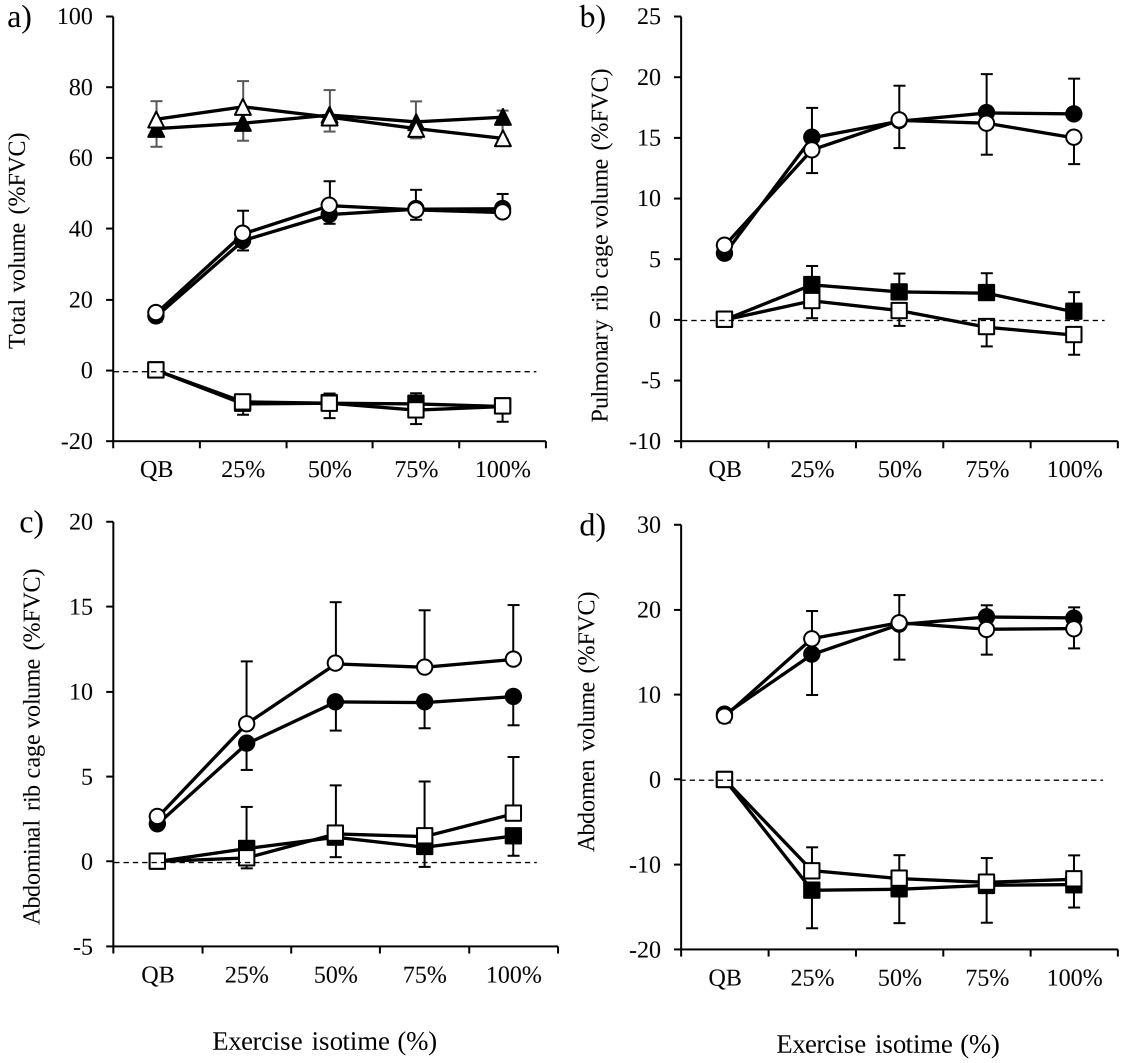
CONTROL GROUP



Changes in inspiratory flow (*a*), expiratory flow (*b*), total time of breathing cycle (*c*), inspiratory time (*d*), expiratory time (*e*), and duty cycle (*f*) within the control group at pre- (*closed symbols*) and post-intervention (*open symbols*) during quiet breathing (QB) and exercise isotime (25%, 50%, 75%, and 100%) in the control group. *denote significant difference from pre-intervention; † significant difference between intervention groups.

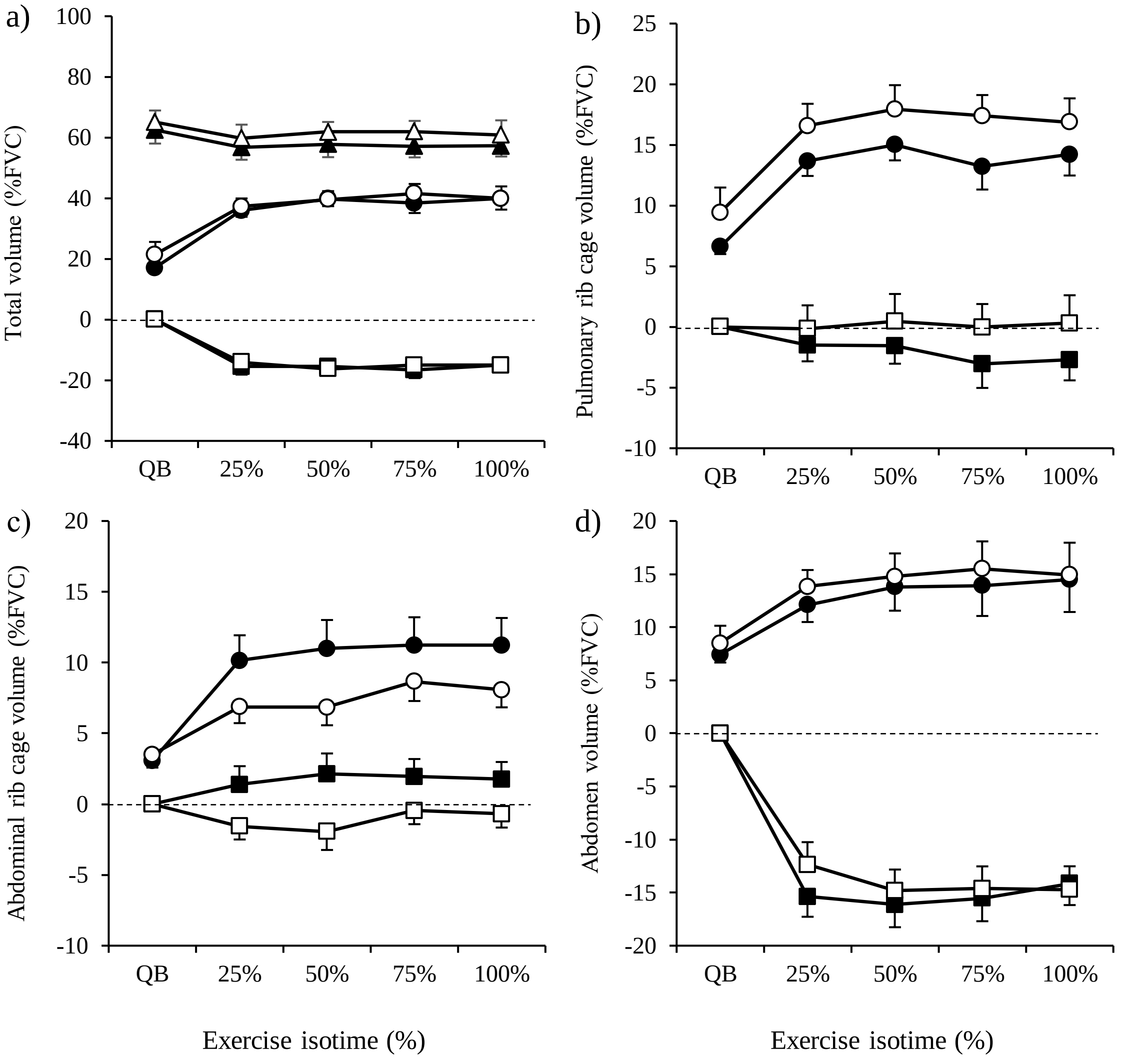
Appendix 9 – Total and compartmental thoracoabdominal end-inspiratory and end-expiratory volumes expressed as %FVC (chapter 6)

INTERVENTION GROUP



Volume changes (expressed as percentages of forced vital capacity; %FVC) of the a) total thoracoabdomen, b) the pulmonary rib cage , c) the abdominal rib cage and d) the abdomen within the IMT group at pre- (*closed symbols*) and post-intervention (*open symbols*) during quiet breathing (QB) and exercise isotime (25%, 50%, 75%, and 100%). *Circles* indicate end-inspiration, *squares* indicate end-expiration and *triangles* indicate chest wall volume at total lung capacity (TLC; $V_{CW, TLC}$). *Dashed line* indicates end-expiratory volume (V_{EE}) at quiet breathing (QB).

CONTROL GROUP



Volume changes (expressed as percentages of forced vital capacity; %FVC) of the a) total thoracoabdomen, b) the pulmonary rib cage , c) the abdominal rib cage and d) the abdomen within the control group at pre- (*closed symbols*) and post-intervention (*open symbols*) during quiet breathing (QB) and exercise isotime (25%, 50%, 75%, and 100%). *Circles* indicate end-inspiration, *squares* indicate end-expiration and *triangles* indicate chest wall volume at total lung capacity (TLC; $V_{CW,\,TLC}$). *Dashed line* indicates end-expiratory volume (V_{EE}) at quiet breathing (QB).

Appendix 10 – The debrief sheet for the control group following the 8-week intervention (chapter 6)

PARTICIPANT DEBRIEF – CONTROL GROUP

Participant code:

Name of Researcher: James Manifield

Name of Supervisors: Dr. Gill Barry / Prof. Ioannis Vogiatzis

Project Title: Effects of inspiratory muscle training on respiratory kinematics and exercise capacity in older adults.

1. What was the purpose of the project?

The purpose of this project was to determine, if any, the differences in exercise capacity and chest wall volume response following an 8-week inspiratory muscle training programme in older adults. Furthermore, physical activity levels and balance ability before and after training were examined along with heart activity during submaximal exercise. We expect to find a greater improvement in respiratory muscle strength and exercise capacity, and potentially increased physical activity levels, improved chest wall volume and heart rate response to exercise, and improved balance following inspiratory muscle training in the ‘strength’ group compared to the control ‘endurance’ group.

There is evidence to support these findings in patients with lung and heart conditions, however, there is very little research investigating the effects of this training in healthy older adults.

2. How will I find out about the results?

Once this study is completed and the data is analysed, the researcher will email you a general summary of the results if requested.

3. **Have I been deceived in any way during the project?**

In this study we informed you that there were two groups: a strength group and an endurance group. We did not expect to see any changes following training in the endurance group and it therefore served as a placebo control. It was presented to you as ‘endurance’ training to ensure adherence to the intervention. If you were in the control group and would like to continue using the device, we suggest that you increase the intensity for maximum benefits.

4. **If I change my mind and wish to withdraw the information I have provided, how do I do this?**

If you wish to withdraw your data then email the investigator named in the information sheet within 1 month of taking part and give them the code number that was allocated to you (this can be found above on this debrief sheet). After this time, it might not be possible to withdraw your data as it could already have been analysed.

The data collected in this study may also be published in scientific journals or presented at conferences. Information and data gathered during this research study will only be available to the research team identified in the information sheet. Should the research be presented or published in any form, all data will be anonymous (i.e. your personal information or data will not be identifiable).

All information and data gathered during this research will be stored in line with the Data Protection Act and will be destroyed 36 months following the conclusion of the study. If the research is published in a scientific journal it may be kept for longer before being destroyed. During that time the data may be used by members of the research team only for purposes appropriate to the research question, but at no point will your personal information or data be revealed. Insurance companies and employers will not be given any individual’s personal information, nor any data provided by them, and nor will we allow access to the police, security services, social services, relatives or lawyers, unless forced to do so by the courts.

If you wish to receive feedback about the findings of this research study then please contact the researcher at james.manifield@northumbria.ac.uk

This study and its protocol have received full ethical approval from Faculty of Health & Life Sciences Research Ethics Committee. If you require confirmation of this, or if you have any concerns or worries concerning this research, or if you wish to register a complaint, please contact the Chair of this Committee (Claire Thornton claire.thornton@northumbria.ac.uk) stating the title of the research project and the name of the researcher: James Manifield.

Appendix 11 - Example transcripts both immediately following the IMT intervention and at 3-month post-intervention (chapter 7)

Interview immediately following the 8-week intervention

Interviewer: James Manifield

Participant: EF (IMT01)

Interviewer: Okay so the purpose of this interview is to kind of get your perceptions and experiences with inspiratory muscle training and the training programme that you've been doing over the past 8 weeks. So to start with, had you heard of inspiratory muscle training before you started with this study?

EF: No, not at all. It was something completely new to me which was why I was happy and wanted to do the trial, it was a very interesting subject.

Interviewer: Very good. So how often do you exercise usually would you say?

EF: Normally 3 times a week but I walk every day so quite regularly.

Interviewer: Yeah. Do you do anything else other than walking or is that your main…?

EF: That's the main thing, yeah.

Interviewer: Okay, good stuff. Would you say that you're fitter than the average person your age or about the same?

EF: Er I think I'm a little bit fitter because of my peer group who are my age do less than I do so based on that I think I'm slightly fitter than them.

Interviewer: Yeah. Er so did you enjoy the training programme?

EF: I did. I really enjoyed it. It was very interesting doing the breathing every morning and every night was something I had to get into a routine to do but when I did it I found it fascinating to see just how far I could push myself so that was really good.

Interviewer: Mmhm very good. Was there anything that you didn't enjoy about the training?

EF: No. I've enjoyed it all because like I say I like walking so I quite like doing the walking trials and doing the bike and stuff. It was really to challenge me more than anything else and I really enjoyed the challenge.

Interviewer: Good stuff. Would you change anything about the actual training?

EF: No. I think it's perfect, it fits the criteria of what you wanted to achieve.

Interviewer: So you'd keep the morning and evening sessions?

EF: Yes I'd keep the morning and evening because as the day goes on obviously your strength weakens sometimes and that you could tell sometimes at night I'd have to put a bit more effort in but still do it so no I think morning and night-time was good.

Interviewer: Great, yeah. So have you noticed any changes from when you started to now after the 8 weeks of training.

EF: Yeah. When I'm at the gym my breathing's a lot better and, better in the sense that it's more controlled whereas before I would breathe at the wrong time. So it's made us very conscious of what I'm doing and what my breathing's like and I think it's a little bit stronger.

Interviewer: Okay.

EF: So it's certainly helped in that respect.

Interviewer: So would you say it's easier to breathe when you're exercising?

EF: Yes, uh-huh. I don't get out of breathe as much as I used to because I think I'm controlling my breathing properly rather than just grasping at it.

Interviewer: Okay.

EF: I'm literally thinking about my breathing whereas before I didn't and I used to get out of breath quite easily whereas now I don't because I'm actually thinking about when I'm breathing so yeah that's helped.

Interviewer: Yeah. What about your quality of life has that just stayed the same over the period or…?

EF: Er I think it's probably stayed the same because I'm doing the same things but I'm not fatigued by any of it. I think doing the breathing exercises has probably helped where I'm getting rid of the stale air and bringing in fresh air whereas before I was probably shallow breathing now I'm actually physically deep breathing instead of that.

Interviewer: Yeah.

EF: So yeah, I suppose it has helped that way but lifestyle wise it hasn't changed.

Interviewer: Okay. So what about your balance? Would you say you have good balance normally?

EF: I think I have. I think I've always had fairly good balance and that come probably because I used to do ballet dancing when I was younger and football but that's not the same sort of thing but I have always had quite good balance and I think that's helped.

Interviewer: Good stuff. Last question, would you plan on keeping using the device after this research is over?

EF: Yeah absolutely, erm because before I came back to do this last one, I actually looked up about purchasing one.

Interviewer: Okay.

EF: To use at home. Because to me it's a very good, not exercise, but a good form of control and I want to see if I can keep that up and not just relax back to old ways where I wasn't breathing properly. So no I would definitely keep using it.

Interviewer: Good stuff. So that's all the questions I need to ask you so thank you very much.

EF: You're welcome.

Follow-up interview at 3-month post-intervention

Interviewer: James Manifield

Participant: EF (IMT01) – IMT group (follow-up)

Interviewer: Okay so these questions that I'm about to ask you are related to your feelings and perceptions towards the training now that the study's over. So the first is have you used the inspiratory muscle training device since the study has ended?

EF: Yes, I have. I've used it quite regularly, erm I've missed one or two days but I've used it at least once a day since the trial finished.

Interviewer: Okay great. So whilst you were using it at home, was this the same protocol you were doing for my study? So the 30 breaths, twice a day?

EF: Yes, I was following what I had done with you and just found it really beneficial.

Interviewer: Perfect, so if I remember correct you were in the strength group?

EF: Uh-huh.

Interviewer: So were you still sort of keeping that same load and increasing it when you found it easy.

EF: Yes I did. There was only a couple of times when I wasn't well that I dropped it down, but I still continued, I just dropped it down a notch. And then once I was better I went back up again.

Interviewer: Great. So what do you think the reasons were that you continued to use this device when you could have sort of stopped using it altogether.

EF: To be honest, I found that it helped with my breathing and certainly with going to the gym, it controlled the way I breathed. So doing exercise was better because I was actually more conscious of how I breathed.

Interviewer: Okay, great.

EF: So it was really beneficial.

Interviewer: Very good. So you say you can control your breathing a bit better.

EF: Yes, uh-huh.

Interviewer: So is that just during exercise? Did you notice any other changes during exercise in terms of do you feel fitter or less breathless or is it just more kind of being able to control the breath?

EF: I feel a lot less breathless and just being on holiday, because I've been to Lanzarote, I actually climbed to the top of the volcano.

Interviewer: Very nice.

EF: And I think the training helped. Er because it really helped with my breathing, I wasn't gasping for breath, I could control it so it meant I could get to the top without much, well not much effort really.

Interviewer: Perfect. Erm, so was the reason that you carried on because you felt that during the actual training you got benefits and you wanted to prolong these benefits or…?

EF: Yeah. Absolutely. I really felt after I had finished I thought that my breathing was better, my overall strength with breathing was better. I just felt it was really beneficial and certainly because I do a lot of walking, I can pace myself better.

Interviewer: Great. That's really good to hear. I think that's all the questions I've got to ask you really.

EF: Oh, that's grand.

Interviewer: So yeah, thank you very much for participating.