**Protocol for Cognitive impairment in chronic obstructive pulmonary disease (COPD):**

**Effects of exercise and exercise training**

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**Name Position Responsibility**

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**Background:**

COPD is a commonly occurring lung disease which has huge health-care costs world-wide. As the population ages, COPD is rarely an isolated condition, but rather accompanied by a number of co morbidities including arthritis, obesity, anxiety and depression and cognitive impairment. (Villeneuve et al, 2012) People with COPD have significantly lower cognitive function compared to normal healthy people (Deering et al, 2016) and the presence of co morbidities makes COPD a more complex condition to self-manage. (Pierobon et al, 2017)

Cognitive impairment is associated with increased mortality and disability and remains poorly understood in people with COPD. (Dodd et al, 2010) It has been reported that people with COPD have a greater risk of developing cognitive impairment than those without COPD (Hung et al, 2009) with the incidenceof cognitive impairment being higher in people with COPD (36%) compared to those without COPD (12%). (Torres-Sanchez et al, 2015) No work has been done to determine the incidence of cognitive impairment in an Australian pulmonary rehabilitation population.

In people with COPD, it has been suggested that hypoxaemia is the crucial factor in the development of cognitive impairment with the incidence reported to be as high as 77% in those with hypoxic COPD. (Chang et al, 2012; Grant et al, 1982) A possible explanation of the higher incidence of cognitive impairment in hypoxic COPD was that hypoxaemia affects oxygen dependant enzymes that are important in the synthesis of the neurotransmitter, acetylcholine. (Heaton et al, 1983) As well, a low peripheral oxygen saturation (SpO2< 88%) has been strongly associated with risk of cognitive impairment and long term oxygen therapy reduces the risk of developing cognitive impairment. (Thakur et al, 2010) This means that people with COPD plus cognitive impairment have more difficulty with cognitive functioning e.g. remembering commands, being able to exercise independently and to self-manage their condition. Therefore identifying cognitive impairment in this population will help clinicians to improve patient care.

Pulmonary rehabilitation programs that include exercise training are an essential part of the management of COPD and have been shown to improve exercise capacity and quality of life in people with COPD. (McCarthy et al, 2015) As well, exercise training has been shown to improve cognitive impairment in people with COPD (Emery et al 1998; Emery et al, 2001, Kozora et al, 2000) One bout of acute exercise training (cycling to peak work by 20 minutes) compared to watching a video showed improvements (n=29) in verbal fluency but reported no change to short-term memory, attention or psychomotor speed and no improvements in video group. (Emery et al, 2001) As well, longer exercise interventions (more like pulmonary rehabilitation) of three weeks (Kozora et al, 2000) and ten weeks (Emery et al, 1998) showed improvements in digit vigilance test (sustained visual attention, p = 0.006), visual retention (visual memory, p = 0.03) and semantic fluency (ability to generate words to a category, p = 0.04. (Kozora et al, 2000) and trail making and digit symbol (Emery et al, 1998).

Previous work has used different assessment tools to measure cognitive impairment and different durations of exercise training. As well pulmonary rehabilitation programs rarely measure cognitive impairment as part of assessment protocols.

In the studies mentioned a number of different tools have been used to measure different aspects of cognitive functions including the Montreal Cognitive Assessment (MoCa). The MoCa has been reported to be a more accurate measure of cognitive impairment than the Mini–Mental State Examination (MMSE) for screening mild cognitive impairment, because of its ability to report executive functions. As well the MoCa has been reported to be able to detect cognitive change over time in a community sample. (Krishnan et al, 2015) People with COPD when assessed with the MoCa were more likely to have cognitive impairment compared to age matched normal (9.5% v. 2.6%, p=0.0006) (Pierbon et al, 2017) There are few studies that have assessed the effect of short or long-term exercise training on cognitive impairment in people with COPD using the MoCa. People with COPD attending pulmonary rehabilitation may have undiagnosed cognitive impairment which may affect their ability to complete tasks, exercise independently and comply with health recommendations. Identifying cognitive impairment using a simple tool such as the Moca will help physiotherapists working in pulmonary rehabilitation to adapt programs to better suit people who have COPD plus cognitive impairment.

Therefore the **aims** of this study in people with chronic obstructive pulmonary disease (COPD) are to determine: 1).the incidence of cognitive impairment compared to healthy age matched population; 2).whether a single bout of exercise affects cognitive impairment compared to quiet sitting; 3).whether an eight-week pulmonary rehabilitation program of exercise training improves cognitive impairment at program completion and six months follow-up.

The hypotheses of the trial are that 1). The incidence of cognitive impairment will be higher than reported in the healthy, age matched population; 2). A single bout of exercise will improve cognitive function; 3). Pulmonary rehabilitation will improve cognitive function.

**Methods:**

**Participants**

Participants with COPD (see inclusion criteria) will be informed about the study before discharge from hospital and at initial assessment at pulmonary rehabilitation by the supervising physiotherapist.

If the participants agree to be part of the trial, the trial will be explained by the physiotherapist, they will be given written participant information and will be asked to sign consent for the study. The chief investigator will answer any questions raised. Participants will be free to withdraw from the study at any time. The study will be approved by the Ethic Committee of SLHD.

**Inclusion:** Participants will be aged > 40 years and have a diagnosis of COPD [FEV1/FVC: <70%; FEV1% predicted <80% (GOLD Criteria)]

**Exclusion:** Participants will be excluded if they have respiratory diseases other than COPD, musculo-skeletal, neurological conditions that affect the ability to exercise or those unable to read and understand English.

**Randomisation**

Study 1 and study 3 will be observational studies. Study 2 will be a randomised study – participants will be randomised using computerised random number generation. The participants will be randomised into treadmill walk or quiet sitting and given the group allocation in opaque envelopes

**Sample size calculation**

**Study 1:** 100 participants

**Study 2:** 68 participants will be required to have an 80% chance of detecting (as significant at the 5% level), a mean increase of 2 points (minimum important difference) (Wong et al, 2017) in the MoCa, assuming a standard deviation of 2.9 points. (Krishnan et al, 2017) **Study 3:** 34 participants will be required to have an 80% chance of detecting (as significant at the 5% level), a mean increase of 2 points (minimal important difference)(Wong et al, 2017) in the MoCa, assuming a standard deviation of 2.9 points. (Krishnan et al, 2017) To account for a drop out of 15%, 39 participants will be recruited.

1. Wong GKC , Mak JSY , Wong A , Zheng VZY , Poon WS , Abrigo J , Mok VCT. Minimum Clinically Important Difference of Montreal Cognitive Assessment in aneurysmal subarachnoid hemorrhage patients. J Clin Neurosci. 2017 doi: 10.1016/j.jocn.2017.08.039
2. Krishnan K, Rossetti H, Hynan LS et al Changes in Montreal Cognitive Assessment scores over time. *Assessment* 2017, Vol. 24(6) 772–777

**Data**

Paper notes will be used for data collection during assessment times. Paper data will be stored in a locked filing cabinet in a locked office in the physiotherapy gymnasium, RPAH and kept for seven years. Once assessments are complete the data will be stored on a registered SLHD database with participants de-identified. The database will be stored on a password protected computer in a locked office in the physiotherapy gymnasium, RPAH.

Data used for publication will be de-identified. Participants will be given a written summary of their results at completion of the study.

**Study design**

**Study 1** will be a short-term observational study to examine the incidence of cognitive impairment in COPD (compared to healthy age matched normal), either at the end of a hospital admission for an acute exacerbation or when stable (at commencement of pulmonary rehabilitation). Participants will complete assessment measures (see below).

**Study 2** will be a randomised study to examine the effect of one bout of treadmill exercise compared to quiet sitting on cognitive impairment in people with COPD. Patients will be recruited from pulmonary rehabilitation and randomised via computerised randomisation generation to either the treadmill group or the quiet sitting group.

Assessment measures (see below) will have been performed as part of Study 1.

Treadmill walking: participants will be asked to walk on the treadmill for 20 minutes at 80% of the average six-minute walk test speed calculated from the better of two six-minute walk tests. At completion of the treadmill walking participants will rest until oxygen saturation, heart rate and breathlessness returns to pre exercise levels. At this point participants will be asked to complete the Montreal Cognitive Impairment Assessment using an alternative version to control for repeated testing. For the quiet sitting, participants will be asked to sit in a quiet room and listen to music of their choice.

**Study 3** will be a short- and long-term observational study to will examine whether an eight-week pulmonary rehabilitation program of supervised exercise training (twice per week) will improve cognitive impairment after completion and at six months follow-up. Patients will be recruited from those referred to pulmonary rehabilitation.

Assessment measures will have been performed as part of Study 1.

Exercise training will include walking and cycle endurance training (total time of 40 minutes) as well as strength training for the upper and lower limbs using weight equipment, free weights and therabands. At the completion of pulmonary rehabilitation and at six months all assessment measures will be repeated.

**Assessment**

Full assessment will be performed at Study 1 (T1), Study 3 (commencement and completion of pulmonary rehabilitation and six-month follow-up, (T3 and T4)) and assessment of cognitive impairment alone will be performed for Study 2 (T2) (Figure 1).

Assessment for all participants will include anthropometric data (age, gender, weight, height, BMI); FEV1/FVC and FEV1% predicted using the EasyOne spirometer; oxygen saturation, heart rate using the Masimo RadV pulse oximeter, breathlessness using the Modified 1 to 10 Borg Scale; functional exercise capacity using the six-minute walk test (6MWT), anxiety and depression using the Hospital Anxiety and Depression Score (HADS) and cognitive impairment using the Montreal Cognitive Impairment Assessment (MoCa).

1. **Cognitive Impairment** will be assessed using the Montreal Cognitive Assessment (MoCA) (Nasreddine et al, 2005) which is readily used in SLHD. MoCA is more accurate than MMSE for screening MCI, probably due to the better ability of the former to detect executive functions compared to the latter. The MoCA has been used as a screening instrument for moderate cognitive impairment by assessing memory, language, executive functions, visuospa­tial skills, calculation, abstraction, attention, concentration and orientation. The MoCA is freely accessible for clinical and educational purposes and is available in 36 languages.
2. **Functional exercise capacity** will be measured using the six-minute walk test as described by Holland et al, 2014. Participants will be asked to walk as far as they can around the 32m track for six-minutes. Participants will be given standardised encouragement each minute. During the walk test they will have continuous monitoring of oxygen saturation and heart rate. Breathlessness will be measured at rest and end exercise using the modified 1 to 10 Borg Scale. Participants will rest for 30 minutes or until oxygen saturation and heart rate return to resting levels. They will then repeat the walk test.
3. **Anxiety and depression** will be measured using the Hospital anxiety and depression score (HADS).
4. **Health related quality of life** will be measured using the St George’s Respiratory Questionnaire.

 **Figure 1:** Study timeline

 T1 T2 T3 T4

 T1

Assessment:

MoCa

Six-minute walk test

SGRQ

HADS

 T2

Assessment:

MoCa

 T3 & T4

Assessment:

MoCa

Six-minute walk test

SGRQ

HADS

 Study 1: MoCA. Study 2: 1 x exercise session.

 Study 3: Commence PR, Complete PR…………………6 months.

**Legend:** T1, T2, T3, T4: assessment times; PR: pulmonary rehabilitation; MoCa: Montreal Cognitive Assessment; SGRQ: St George’s respiratory Questionnaire; HADS: Hospital Anxiety and Depression Score.

**Expected outcomes from the study**

It is expected that people with COPD will have more cognitive impairment than healthy matched normal and that exercise (one bout or an eight week pulmonary rehabilitation program) will improve cognitive impairment. By identifying cognitive impairment in people with COPD at pulmonary rehabilitation, we will be able to modify programs to better suit participants.

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