PROTOCOL

PROJECT SUMMARY

Neural respiratory drive in patients with pulmonary hypertension, its correlation with disease severity and how it changes with therapy

GENERAL INFORMATION

Chief Investigator

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RATIONALE AND BACKGROUND INFORMATION

Pulmonary hypertension is a rare and progressive condition. It results in significant symptom burden for patients. Despite advancements in medical therapy, it remains a debilitating disease.

Patients with the condition remain under follow up at specialist centres. Initial diagnosis involves invasive tests that measure the pressure inside the blood vessels in the lungs. Follow up of the patients involves less invasive measurements; at the Scottish Pulmonary Vascular Unit (SPVU), this would be 6 minute walk test and blood tests.

Neural respiratory drive (NRD) is a novel physiological marker that is calculated by measuring parasternal electromyogram (EMG). This is a measure of the electrical signals sent by the brain to the muscles either side of the breast bone. It is not possible to measure the output of brainstem neurons involved with respiration directly but EMG of respiratory muscles provides a way of calculating NRD by measuring the myoelectrical signals of the respiratory muscles. Studies have been performed to show that measuring parasternal muscles gives similar results to measuring diaphragm EMG while having the advantage of being non-invasive(1).

Parasternal EMG recordings have been used in research involving patients with cystic fibrosis(2) and chronic obstructive pulmonary disease(3). In these conditions, it has been shown to be a useful marker for assessing response to treatment and as a risk stratification tool in predicting which patients are more likely to have clinical worsening.

In patients with pulmonary hypertension, it would be useful to develop a non-invasive measurement that could potentially be used to guide clinical decision making. EMG is a measurement that can be taken quickly and is non-invasive. It has not previously been studied in patients with pulmonary hypertension.

Our study would provide baseline data on neural respiratory drive in patients with pulmonary hypertension. In addition to acquiring novel data in NRD in patients with pulmonary hypertension, our study would aim to investigate for correlation between change in neural respiratory drive and change in clinical condition, both measured by clinical assessment and by the clinical investigations

already used in standard care. This would be following commencement treatment for pulmonary hypertension as decided by MDT. This may include medications or, in some cases, surgery.

We hypothesise that neural respiratory drive is raised in patients with pulmonary hypertension, correlates with the severity of the disease and changes with therapy.

STUDY GOALS AND OBJECTIVES

To assess neural respiratory drive in patients under investigation for potential pulmonary hypertension.

To assess change in neural respiratory drive following intervention for pulmonary hypertension. (Interventions will include medications and/or surgery. These interventions represent the normal clinical care of the patients involved.)

To correlate any change in NRD with other clinical parameters measured as part of normal diagnostic process (for baseline measurements) or further non-invasive tests (as part of follow up)

STUDY DESIGN

We propose two observational studies

1. Cross-sectional study to assess patients during their diagnostic admission.
2. Following this, some patients will be commenced on therapy as decided by multidisciplinary team. In these, we will look for longitudinal changes in NRD. These changes will be compared to other results obtained as part of normal clinical care to look for any association.

Inclusion criteria

- Age 18 and above
- Able to give informed consent
- Patients being investigated for pulmonary hypertension

Exclusion criteria

- Unable to provide consent
- Patient is pregnant
- Patient has a diagnosed neuromuscular disorder

METHODOLOGY

Patients will be recruited from the Scottish Pulmonary Vascular Unit based at Golden Jubilee National Hospital. Patients referred to the centre are admitted for 4 days to undertake tests in order to formulate a diagnosis. We propose adding an additional, non-invasive test to this to assess neural

respiratory drive. Patients will be approached by one of the research nurses and given information about the study.

Neural Respiratory Drive

NRD can be assessed by measuring parasternal electromyogram (Dual Bio Amp, ADInstruments, Oxford, U.K.). Readings are taken by applying two small electrodes in the second intercostal space either side of the sternum and one to the shoulder. The electrodes are similar to those used in ECG acquisition. A thin belt is worn round the chest to assess respiratory rate. The patient will also breathe through a mouthpiece so that flow measurements and respiratory rate can be measured. Measurements are then taken during normal breathing and also during maximal breathing effort ('sniff' procedure). Tests may be taken with patient recumbent at 45 degrees and supine. The test is non-invasive, has been safely performed in patients in previous studies and is not anticipated to cause any harm or distress. The total time for measurements will be around 20 minutes per patient.

NRD will be calculated as root mean square of normal tidal breathing as a proportion of maximal inspiratory effort (maximum inspiration from functional reserve capacity, taken as a sniff manoeuvre).

At the end of the inpatient stay for diagnosis, some patients are commenced on treatment and followed up in clinic. It would be our intention to reassess these patients at clinic to test NRD and compare how this changes over time compared to other clinical parameters.

Information will be collected from case notes from baseline investigations. This will include:

- 6 minute walk distance (6MWD) with breathing perception score
- Pulmonary function tests (FEV1, FVC, DLCO, TLC, Va)
- Right heart catheterisation
- NTproBNP
- WHO Functional Class
- Quality of life (QoL) questionnaire – emphasis 10, CAMPHOR
- Cardiopulmonary exercise test (CPET) – peak work rate, peak VO_2, VE/VCO_2.
- Height, weight, BMI

All of the above investigations are acquired as part of standard clinical care during inpatient stay.

Information will be collected from follow up investigations when patients return for routine clinic appointment. This will include:

- 6MWD (with BORG)
- QoL – emphasis 10, CAMPHOR
- WHO functional class
- NTproBNP

Again, the above tests are acquired as part of standard clinical care at routine follow up.

In addition, we will collect further readings of NRD in these patients when they attend for their standard follow up appointment. For the majority of patients, this will be after 3-4 months. For a subset of patients with chronic thromboembolic pulmonary hypertension, this may be up to one

year after initial readings because these patients may be suitable for surgical intervention, which is not done locally and usually takes place 6-12 months after diagnosis at SPVU.

As such, we intend that a patient will take part in the study for 52 weeks maximum, with most patients taking part for 16 weeks, and the study will not require them to have any additional attendances at hospital outwith their standard hospital admission for diagnosis and clinic follow up.

SAFETY CONSIDERATIONS

The tests/interventions performed as part of the study are in addition to the tests the patients will receive as part of standard care are:

- NRD measurement via parasternal EMG recordings

Parasternal EMG is a non-invasive test that is well tolerated and does not cause any distress. It requires around 20 minutes for each patient on each occasion.

FOLLOW UP

Patients will be followed up in clinic as part of their standard care. This will continue beyond the duration of the study.

DATA MANAGEMENT AND STATISTICAL ANALYSIS

Data will be stored on NHS password encrypted computers. They will be analysed using Microsoft Excel and SPSS.

EXPECTED OUTCOMES

Novel cross-sectional and longitudinal data about neural respiratory drive as assessed by EMG measurement in patients being investigated for pulmonary hypertension.

Changes in NRD in patients following intervention (medicine and/or surgery).

DURATION OF PROJECT

The study is proposed to last for 24 months.

Recruitment – 120 patients with baseline measurements with longitudinal follow up proposed on 60 patients, taking into account patients who may not be followed up following diagnosis and patients who may be lost to follow up.

POWER AND STATISTICAL ANALYSIS

There is limited data of EMG measurements in patients with pulmonary hypertension previously. Using results from a similar patient group with chronic obstructive pulmonary disease (4), change in NRD in patients who clinically improved after treatment showed a reduction in EMG measurements of 4%. The baseline measurement in the patient group was 20.3% (EMG of tidal breathing as a percentage of maximum effort) with a standard deviation of 9.9. Taking these figures into account with a power of 80% and confidence level of 0.05 would give a sample size of 49.

REFERENCES

1. Reilly CC, et al. Neural respiratory drive, pulmonary mechanics and breathlessness in patients with cystic fibrosis. Thorax 2011; **66**: 240–246
2. Reilly CC, et al. Measurement of parasternal intercostal electromyogram during an infective exacerbation in patients with cystic fibrosis. European Respiratory Journal 2012 40: 977-981
3. Jolley CJ, Luo YM, Steier J, et al. Neural respiratory drive and breathlessness in COPD. Eur Respir J 2015;**45**: 355–364
4. Murphy PB, Kumar A, Reilly C, et al Neural respiratory drive as a physiological biomarker to monitor change during acute exacerbations of COPD Thorax 2011;66:602-608.

NRD FLOWCHART