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Title

The Role of Cardiopulmonary Exercise Testing in people with Heart Failure with Preserved Ejection Fraction

Investigators

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Study Protocol

Ethical approvals from Ulster Research Governance, REC NI and SEHSCT were obtained. The data collection for this cross-sectional study was conducted at the Cardiology department of Ulster hospital between July 2024 to July 2025.

Study population and recruitment process:

Medical records of patients with suspicion for heart failure with preserved ejection fraction were screened by the Staff Grade Cardiology Registrar (direct healthcare team) under the supervision of the Principal Investigator, Dr. Peter McKavanagh (Cardiologist) at the participating site (Ulster Hospital, Dundonald). This screening was based on the following inclusion and exclusion criteria.

Inclusion Criteria

- Males and females
- Age ranged between 18 – 80 years.
- Clinical suspicion of heart failure with preserved ejection fraction
- Ejection Fraction of ≥50% on the most recent Echocardiogram
- Ability to undertake leg exercise without any impediment

Exclusion Criteria

- Ejection fraction <50% on echocardiogram
- Hospital admission in the past 6 months
- Female subjects that are knowingly pregnant or believe they may be pregnant
- Contra-indication of CPET: myocardial infarction, unstable angina, uncontrolled arrhythmias, moderate to severe valvular stenosis, acute infection, acute endocarditis and history of syncope.

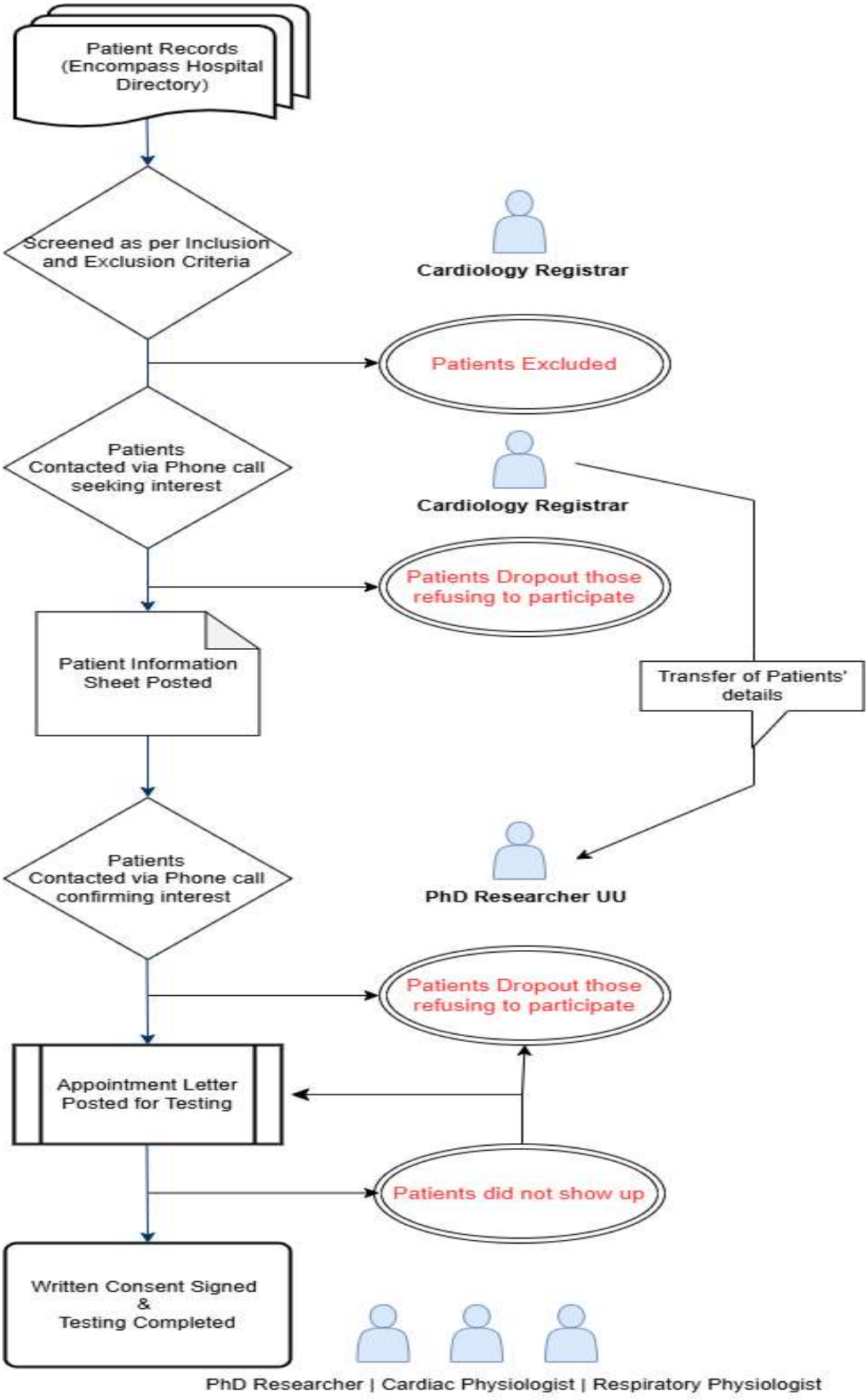
Recruitment and informed consent -

The screened patients were contacted via phone call by the member of the direct healthcare team, informing them about the research project, seeking their verbal consent to receive patient information sheet (PIS). The participant information sheet (PIS) (Annex-1) was posted out to these patients containing information related to the investigation, the conduct of the test, potential risks and benefits, and potential of identifying new undiagnosed condition.

The contact details and past medical history of the patients were shared with the external research team (PhD researcher, Ulster University). The transfer of data took place using secured, password protected organizational email ID.

These patients were given a period of 5 days (cooling off period) to read through the PIS and decide whether they would like to volunteer for the study or not. After 5 days, these patients were contacted via phone call by the PhD researcher and those agreeing to participate in the study were scheduled for an appointment to the hospital. The pre-requisites of the exercise test are re-stated verbally, that includes avoiding strenuous exercise, tea, coffee, smoking and alcohol on the day. The participants are advised to take regular medications for the day and wear appropriate clothing (i.e loose fitted clothes and running shoes).

Recruitment Process.



Cardiopulmonary Exercise Testing (CPET) Protocol :

CPET Team:

Member	Name	Designation	Role
1	Saqib Javaid	Medical Doctor & PhD Researcher	Overall CPET Lead
2	David Moorehead	Cardiac Physiologist	ECG Monitoring
3	Gemma Moss	Respiratory Physiologist	Spirometry, Patient interaction during CPET

CPET Testing Protocol

The testing protocol was divided into 5 phases: spirometry, CPET preparation, resting baseline, warm-up, increasing the workload, and recovery.

i- Spirometry:

The assessment involved measurements of forced expiratory volume in the first second (FEV1), forced vital capacity (FVC) and their ratio (FEV1/FVC). These measures help identify any pre-existing respiratory limitations that could influence CPET results. The CPET software system automatically calculates the maximum voluntary ventilation (MVV) using the FEV1 value from the spirometry using the formula MVV = FEV1 x 40. The MVV calculated is used as a reference for respiratory reserve during CPET.

ii- Preparation phase:

Gas and volume calibration was carried out. Patient details including age, biological sex, weight, height was entered in the CPET software. Calculation of Incremental workload protocol is done using the Wasserman's formula:

$$W = \frac{PredVO2max - VO2unloaded}{103}$$

The participant was asked to mount the cycle ergometer, and a facemask is attached covering the mouth and nose. The participant was instructed not to speak during the test and communicate only using hand movements to avoid artifacts. The disposable chest and limb electrodes was attached to the participant for ECG recording and a ear lobe pulse oximeter was attached.

Resting baseline

The participant rested on the cycle ergometer without movement to record the baseline readings and minimize alterations caused by anxiety.

Unloaded cycling (warm-up)

The participant was asked to pedal along for 3 minutes with the cycle ergometer unloaded. The participant was advised to keep the cadence (RPM) between 60 to 65 at all times of the test.

Increasing workload

Lasting 10 ± 2 minutes, this phase involved a gradual (ramped) increase in exercise intensity. The workload (resistance required to turn the flywheel) increased at a pre-defined/calculated rate for the duration that the patient was able to continue cycling. The patients were motivated to keep cycling while keeping the cadence above 55 rpm at all times. Blood pressure recordings at 2 minutes interval at the initial segment of the phase followed 1 minute interval once the respiratory exchange ratio was seen to cross 1.0 mark. The perceived exertion assessed via the Borg-10 scale was recorded at 4 minutes into the test and as close to maximal exhaustion as possible. The test was switched to recovery phase at the point where the patients raised their hand signaling, they were maximally exhausted.

Recovery

The recovery phase lasted for 3-5 minutes during which the load on the bike was reduced to zero watts while patients continued to cycle at the same cadence. Serial BP readings were taken at every 2-minute intervals. The test was terminated once VO2 had returned to 50% of the peak values or the heart rate and systolic BP return to within the 20 beats/min and 20mm Hg of the pretest resting values respectively.

Post-CPET workflow analysis

After the CPET is concluded and the patient has left, the CPET software is switched to workflow mode. In the workflow mode, the preliminary basic analysis is done as the software guides through different stages of the workflow mode. The peak values, ventilatory thresholds and the slopes are confirmed manually by adjusting the areas on the curved out of which the software identifies and reports those values. Once in place, the software generated a preliminary report that can be saved into the system.

Statistical Plan

Data was analyzed using SPSSv29. Continuous variables were assessed for normality using the Shapiro-Wilk test and visual inspection of histograms and Q-Q plots. Normally distributed continuous variables are presented as mean ± standard deviation (SD), while non-normally distributed variables are presented as median (interquartile range). Categorical variables are presented as frequencies and percentages.

For normally distributed continuous variables, independent samples t-tests were used to compare differences between two groups. For non-normally distributed continuous variables, the Mann-Whitney U test was applied. Categorical variables were analyzed using chi-square tests.

Relationships between continuous variables were examined using Pearson's correlation coefficient for normally distributed variables and Spearman's rank correlation for non-normally distributed variables. Statistical significance was set at $p<0.05$ for all tests.

Appendices

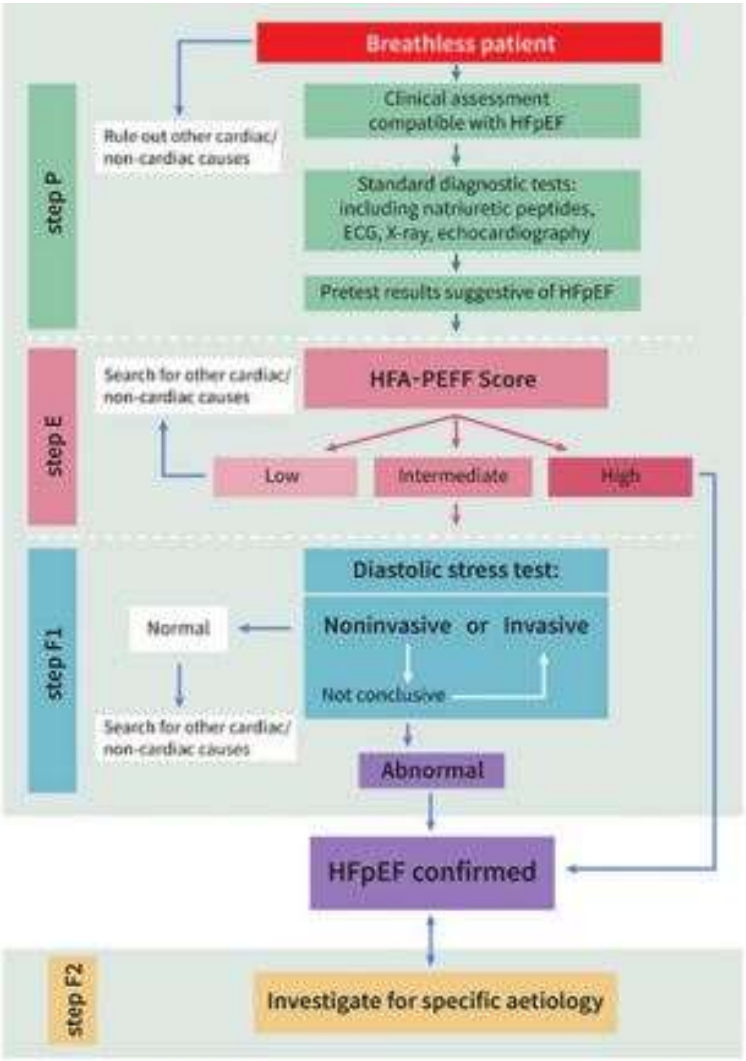


Figure 10: Diagnostic algorithm proposed by HF and ESC.

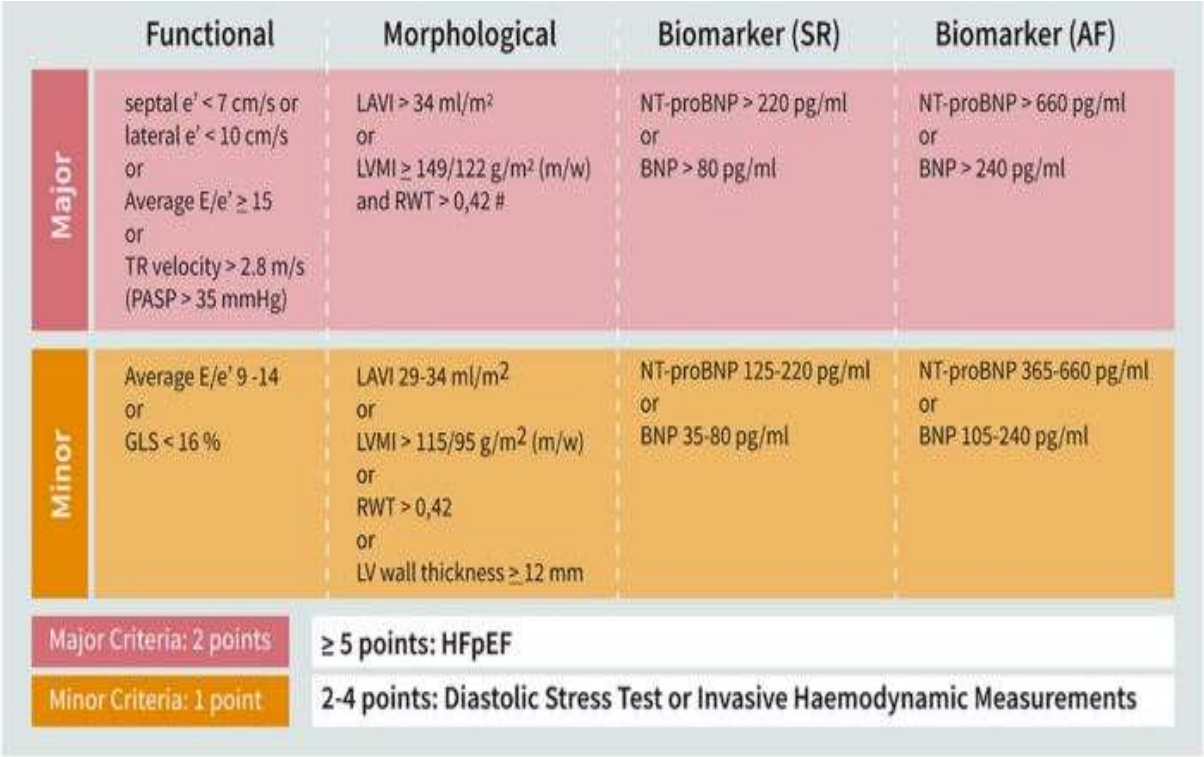


Figure 11: Scoring system for diagnosis of HFpEF .

Figure 12: Flyer shared to facilitate patient & public involvement.

Annex- 1

Participant Information Sheet

Hi,

Please read the information below and answer questions at the end.

Invitation

You are being invited to take part in a research project being conducted in the Cardiology Lab at Ulster Hospital. Before you decide whether or not to participate, please read the following information and do not hesitate to ask any questions about anything that is unclear to you.

What is the purpose of the study?

To find out how people with certain heart related problems respond during an exercise test. This will help our understanding of your condition, its causes and potential treatments in the future.

Who has been invited to participate?

All patients ranging from 18 to 80 years registered with the South-eastern Health and Social Care Trust in Northern Ireland with a clinical suspicion of heart related problems are invited to participate.

What the participation will involve?

If you are interested in taking part in this study, you will be asked to complete a consent form and provide contact details prior to participation.

- You will be invited to visit the Cardiology Lab at the Ulster Hospital. The day and time of will be mutually agreed beforehand. Directions to the lab and things to carry along will also be conveyed at the time of booking the visit. You will be provided with a pre-validated parking ticket.
- You will be asked to read the consent form before signing it. Any related queries will be welcomed.
- A familiarization session will be delivered in which you will be demonstrated how the exercise test will be performed. This will take approximately 30 minutes.
- If you require further time to make up your mind, a second visit will be booked. If you are

happy to proceed with the testing preparation will be made accordingly. You will be asked to perform the test on an exercise bike for about 8 to 12 minutes. During the test, you will be breathing in a mask covering your nose and mouth. An elastic belt will be worn around the chest with a heart sensor at the front. Four other sensors will be attached to the front of the chest to monitor your heart. There will be qualified clinical staff with you at all times.

- You will be guided about the pre-requites of the exercise test well before the testing day. These include avoiding strenuous exercise, smoking, tea and coffee 24 hours before the test. On the day of the exercise test, you should arrive wearing appropriate clothing and footwear (T-shirt and Joggers).
- The exercise test will be postponed if you have fever, cold, cough or any sign of infection.

Who has sponsored and reviewed this study?

This research project is sponsored by Ulster University. The study has received ethical approval from filter committee and research governance of Ulster University as well as approved from the Research Ethic Committee Northern Ireland (REC NI).

Benefits:

Taking part in the research will give you information of your condition and your symptoms. We will give you feedback on your current level of fitness and working towards a healthier lifestyle. Your participation will also help us to understand certain heart conditions which could inform future treatments. There is also a possibility of identifying any other potential health related findings related to lungs and muscles.

Risks and/or disadvantages of taking part?

There is very little risk associated with taking part in this study. It is normal to feel out of breath during the test and muscles may be sore after the exercise test or the day after. Some participants may feel chest discomfort, faint, abnormal rise in blood pressure and abnormal heart rhythm. In extremely rare cases there is a risk of sudden cardiac arrest. **The accompanying hospital staf f and research team are fully trained and equipped to promptly respond and tackle any events.**

Do I have to take part?

It is completely up to you to decide whether or not you take part. If you decide to participate, you will be given this information sheet to keep, and you will be asked to provide contact details and sign a consent form.

Will my taking part in this study be kept confidential?

All information collected for the study will be kept strictly confidential, in accordance with General Data Protection Regulations (GDPR) rules and will be kept for 10 years. The research data will be coded so that you cannot be identified, and the data will be held on password protected computers. Your name, address and personal details will not be made available to any organization beyond the study team. It is intended that the findings from this study willbe published in scientific or medical journals and presented at conferences. You will **not** be identified in any report or publication.

Where can you find out more about how your information is used?

You can find out more about how we use your information.

- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team
- by sending email to our data protection officer, Eoin Coyle, at e.coyle2@ulster.ac.uk or ringing at 02871675525

What happens when the study end?

You will be contacted by a member of your direct care team (doctor or staff nurse) from the hospital informing you about the study results. This might also include any other potential health related findings/issues identified.

Right to withdraw:

You can stop being part of a research study at any time, without giving a reason. You can do so by informing the principal investigator, Dr. McKavanagh through his secretary via the phone (028 9048 4511 ext 21762) or by email (Wendy.Wratten@setrust.hscni.net). A decision to withdraw, or a decision not to participate, will not have any implications. on the healthcare services being provided to you. If you withdraw from the research team will keep the research data about you that they already have. You can find out what would happen with your data before you agree to take part in a study.

Who can I contact if I have a complaint?

If you want to complain about how researchers have handled your information, you should contact the research team. If you are not happy after that, you can contact the Data Protection Officer Eoin Coyle, at e.coyle2@ulster.ac.uk or ringing at 02871675525. Furthermore, related information for submitting a complain through the Trust can be accessed at https://setrust.hscni.net/wp-content/uploads/2020/08/How-to-Make-a-

Complaint-English-V10.1-Aug-2020.pdf.

Contact details of local Principal Investigator

Dr Peter McKavanagh
Secretary: Wendy.Wratten@setrust.hscni.net Tel: 028 9048 4511 ext 21762

Thank you for taking the time to read this information. Please read the following questions and answer accordingly.

Q.1 Are there any aspects that needs further clarification? Is there anything else you would like to know about?

Q.2 Is there anything you want us to omit or change?

Q.3 After going through the contents above, would you be encouraged to participate in this study?

Instructions for Testing Day

Please abide by the following instructions when you visit the hospital for the testing:

- Arrive at the hospital 5 min before the appointment time.
- Avoid strenuous exercise, tea, coffee, smoking and alcohol on the test day.
- Continue taking your usual medications.
- Wear appropriate clothing (i.e. loose fitted clothes and jogging shoes).

Consider postponing the test in case you have any one of the following:

- Fever
- Cold
- Cough
- or any sign of infection

In case of any appointment related query or changes, please inform Dr. Javaid as soon as possible using the contact details stated below.

Contact details:

Dr. Saqib Javaid

07869195234

javaid-s2@ulster.ac.uk

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