Effects of breaking up sitting time on cardiometabolic risk markers and cardiac function post myocardial infarction.

SHORT STUDY TITLE / ACRONYM

The MOVE-MI study

PROTOCOL VERSION NUMBER AND DATE

V6.0/ 12May20

RESEARCH REFERENCE NUMBERS

IRAS Number:	265468
SPONSORS Number:	N/A

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature: Date:

..../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature: Date:

..../...../.....

Name: (please print):

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Funder(s)	N/A
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Committees	N/A

STUDY SUMMARY

Study Title	Effect of breaking up sitting time on cardiometabolic risk markers and cardiac function post myocardial infarction.
Internal ref. no. (or short title)	The MOVE-MI study
Study Design	Randomised, cross-over trial
Study Participants	Low risk patients with a first uncomplicated myocardial infarction
Planned Size of Sample (if applicable)	23 participants
Follow up duration (if applicable)	N/A
Planned Study Period	1 year
Research Question/Aim(s)	Does breaking up sitting time in patients following a myocardial infarction improve their cardiometabolic risk markers and cardiac function?

ROLE OF STUDY SPONSOR AND FUNDER

The Sponsor of this study is the University of Bedfordshire. The sponsor is responsible for the overall conduct and management of the study

There is no external funder for this study.

ROLES AND RESPONSIBILITIES OF STUDY MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Cardiac Rehabilitation Team at Bedford Hospital

Regular meetings will be held between the Bedford Hospital Cardiac Rehabilitation team and the study investigators to discuss how to conduct the study in terms of participant recruitment, data collection and dissemination.

Patient and Public Involvement

Prior to the commencement of the study, a PPI group study session will be held with post MI patients to discuss the study design and coordination. This will help the research team to understand any difficulties with recruitment that they may face, as well as how best to conduct the study. Here, they will also be shown any patient facing documents to ensure they are suitably aimed at the target population.

PROTOCOL CONTRIBUTORS

Abbie Bell

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Responsibilities: Study design, study conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

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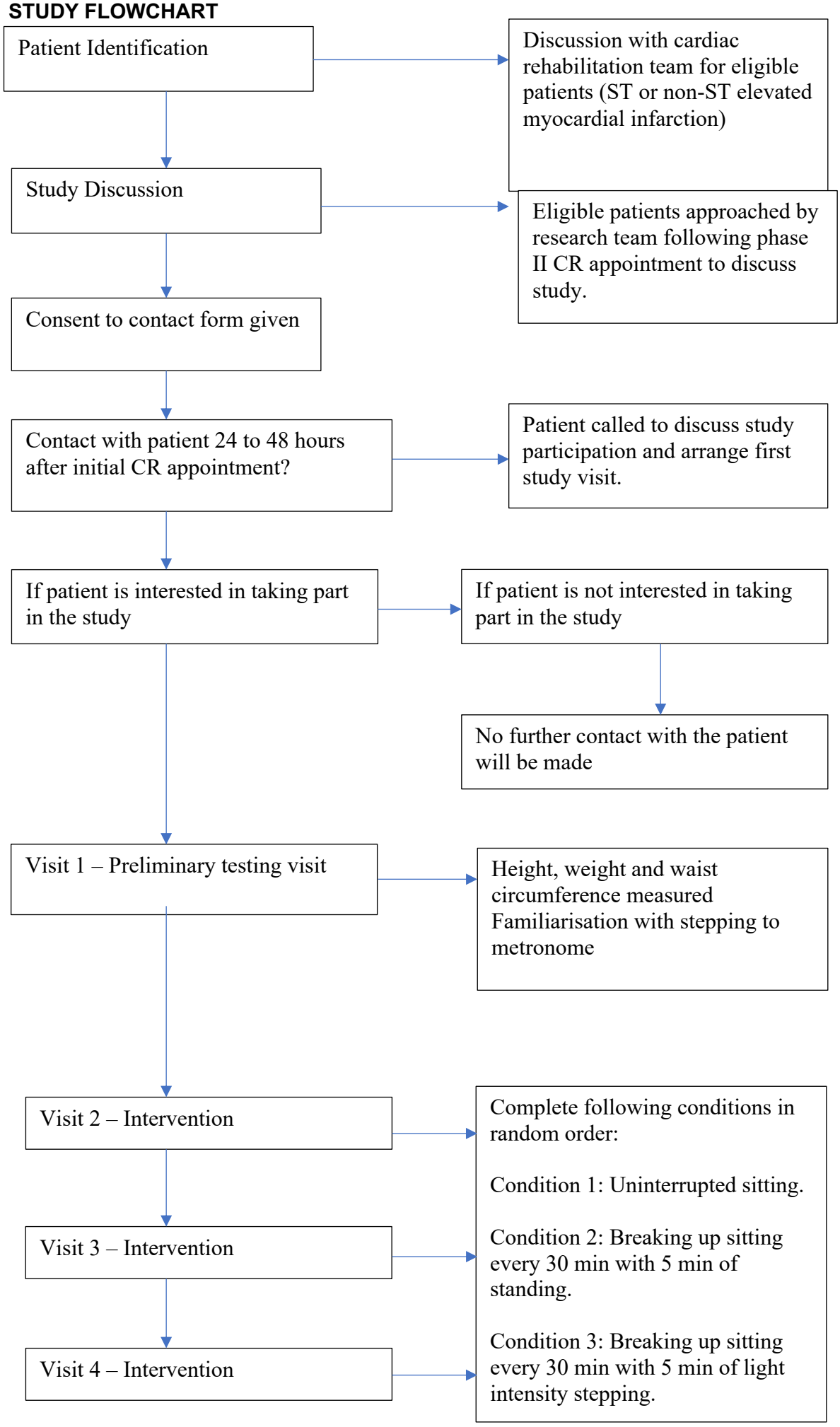
Responsibilities: Overview of study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

KEY WORDS: Post- myocardial infarction (post-MI), Cardiac Rehabilitation (CR), sedentary behavior, cardiometabolic risk

STUDY FLOWCHART



STUDY PROTOCOL

1 BACKGROUND

Cardiovascular Disease (CVD) is the leading causes of mortality and morbidity globally (World Health Organization, 2019). In the UK alone, it was accountable for 124,641 deaths in 2017. Further to this, CVD contributes to a vast economic burden, costing the National Health Service (NHS) £19 billion annually. This is mainly due to a significant number of hospital readmissions following a first cardiac event (198,000 per annum) (British Heart Foundation, 2018).

Following a myocardial infarction (MI), an individual is at an increased risk of a secondary event (20-50% higher risk post MI), compared to those with no prior CVD (Kerr, et al., 2009). Guidelines therefore recommend close management of cardiometabolic risk markers to reduce the risk of a secondary event, with a particular focus on lipid profile and glucose control (European Society of Cardiology, 2019). Poor metabolic health (including impaired lipid and glucose metabolism and high blood pressure levels) is strongly associated with CVD. In turn, there is an increase in insulin resistance and pro-atherogenic markers within the blood that causes endothelial dysfunction. This contributes to the progression of atherosclerosis and thus increases the risk of CVD (Dimina and Mariotti, 2019; Oikonomou, et a., 2019).

There is a linear relationship between both fasting and 2 hour glucose levels with CVD, independent of insulin resistance and type 2 diabetes mellitus (T2DM) (Ning, et al., 2010). A meta-analysis found that, after adjusting for other cardiovascular risk factors, higher blood glucose (both fasting and 2 hour) was positively correlated to the development of CVD, thus suggesting that the more poorly glucose was controlled, the more likely an individual is to develop CVD. Further to this, both triglycerides and blood pressure (BP) showed a likewise association with CVD (Ning, et al., 2010). It is therefore essential to appropriately manage these cardiometabolic risk markers to reduce the risk of secondary cardiovascular events occurring.

Cardiac Rehabilitation (CR) is a secondary preventative measure to further cardiac events. The British Association of Cardiovascular Prevention and Rehabilitation (BACPR) defines CR as ‘the coordinated sum of activities required to influence favourably the underlying cause of cardiovascular disease, as well as to provide the best possible physical, mental and social conditions, so that the patients may, by their own efforts, preserve or resume optimal functioning in their community and through improved health behaviour, slow or reverse progression of disease’. It is suggested by the National Institute for Health and Care

Excellence (NICE) that all patients should be offered a CR programme with an exercise component following an MI (BACPR., 2017).

There is conflicting evidence regarding the benefits of exercise based CR upon cardiovascular mortality and morbidity, hospital readmissions and all-cause mortality. Previously, CR has been shown to be beneficial in longer term health outcomes of cardiac patients. The 2016 Cochrane Review of Exercise based CR found that, when compared with a no exercise control group, exercise based CR accounts for an estimated risk reduction of 26% and 18% for cardiovascular mortality and hospital admissions respectively, but no reduction in total mortality or further cardiovascular events (Anderson, et al., 2016).

However, delivery and structure of CR programmes vary significantly across the country. The British Association for Cardiovascular Prevention and Rehabilitation (BACPR) recommends that 'the patient should receive individual guidance and advice on active daily living together with a tailored activity and exercise plan with the collective aim to increase physical fitness, as well as overall daily energy expenditure and decrease sedentary behaviour' (BACPR, 2017). Despite recommendations to reduce sedentary behaviour, suggestions on how to do so are currently non-existent. Sedentary behaviour is defined as a waking energy expenditure of $\leq$1.5 METs (metabolic task equivalent) while in a seated, reclined or lying posture (Tremblay, et al., 2017). Independent of physical activity levels, high amounts of daily sitting is a risk factor for CVD (Bailey et al., 2019)).

Studies show that breaking up sitting time can reduce cardiometabolic risk markers, thus reducing CVD risk. Within the US National Health and Nutrition Examination Survey (NHANES) study, a detrimental linear association was found between total time spent sitting and waist circumference, high density lipoprotein cholesterol (HDL-C), triglycerides, insulin, insulin sensitivity and β cell function. In addition, independent of total sitting time, a higher number of breaks in sitting per day was significantly beneficially associated with waist circumference, C-reactive protein and fasting plasma glucose. Therefore, both reducing total sitting time and frequently breaking up prolonged periods of sitting are associated with improved cardiometabolic risk in the general population (Healy, et al., 2011).

There is consistent evidence to suggest that breaking up sitting time with 2-5 minutes of light or moderate intensity walking every 20-30 minutes reduces postprandial glucose (Benatti et al., 2015). For example, a randomized cross-over design study conducted by Bailey and Locke (2015) found that breaking up sitting with 2 minutes of light physical activity every 20 minutes reduced postprandial glucose by 16%, but breaking up prolonged sitting with 2 minutes of standing every 20 minutes did not. In participants with impaired metabolic health (e.g. overweight/obese, impaired glycaemia, and people with T2DM), findings have shown

that breaking up sitting time with both standing and light physical activity have benefits on postprandial cardiometabolic risk markers (including blood pressure, glucose, insulin and triglycerides) (Henson et al., 2016; Dempsey et al., 2016). For instance, a study in dysglycaemic, overweight, postmenopausal women found that breaking up sitting time with 5 minutes of standing every 30 minutes resulted in a 34% reduction in postprandial glucose incremental area under the curve (iAUC). Breaking up sitting with 5 minutes of light-intensity self-paced walking (10-12 on the Borg Rating of Perceived Exertion [RPE] scale) every 30 minutes resulted in a 28% reduction in glucose iAUC. Similar effects were seen for insulin iAUC, which was reduced by 20% with standing breaks and 37% by light intensity walking breaks (Henson, et al., 2016). In patients with T2DM, improvements in postprandial cardiometabolic risk markers (glucose, insulin and triglycerides) were seen when sitting was interrupted with light intensity walking (3 minutes every 30 minutes) and simple resistance exercises (3 minutes every 30 minutes). Overall, there was a reduction in postprandial glucose iAUC of 39% in both conditions and postprandial insulin iAUC by 36% and 37% in the light-intensity walking condition and resistance activities conditions, respectively. Postprandial triglycerides were also significantly attenuated in the simple resistance activities condition, but not in response to light-intensity walking breaks. Light-intensity walking and resistance exercise breaks also resulted in a significant reduction in systolic and diastolic blood pressure (Dempsey, et al., 2016). To our knowledge, there have been no studies conducted to date evaluating the effects of breaking up prolonged sitting on cardiometabolic risk markers in cardiac patients.

In addition to poor cardiometabolic health following an MI, an individual can develop structural problems within the myocardium due to myocardial damage and necrosis (Thygesen, et al., 2007). If not managed appropriately, this causes left ventricular (LV) hypertrophy and reduced LV ejection fraction, thus resulting in LV remodeling (Azvedo, et al., 2016). This leads to poor prognostic outcomes for the individual, ultimately resulting in chronic heart failure. This can include shortness of breath, decline in functional capacity and difficulty with active daily living tasks, as well as mental health problems and poor health related quality of life (Lesman-Leegte, et al., 2009). Therefore, interventions need to be identified to prevent these myocardial changes following an MI.

Data from the Bogalusa Heart study suggests that individuals with metabolic syndrome had significantly higher values for LV mass, end-diastolic posterior wall thickness, septal wall thickness and LV end diastolic diameter (Patel et al., 2009). Further to this, high blood pressure, high fasting glucose, high triglycerides and low HDL-C are independently associated with eccentric hypertrophy of the LV. As breaking up sitting time can acutely improve cardiometabolic risk markers, it is plausible that there could be benefits to cardiac function as

well. This would be of great importance to cardiac patients who are at high risk of suffering a secondary event and thus requires evaluation.

2 RATIONALE

While there is extensive research into the effects of exercise based CR upon secondary health outcomes, little is known regarding the effects of breaking up sitting time on cardiometabolic risk markers or cardiac function in individuals that have suffered a cardiac event. Despite BACPR recommending to reduce sedentary behaviour within this population, CR programmes are vague when addressing this health behavior and evidence does not exist to appropriately inform programmes in this respect. In healthy, overweight/obese and Type 2 diabetic individuals, it is known that breaking up sitting time acutely improves postprandial cardiometabolic risk markers. However, no research has evaluated the effects of breaking up sitting time on these biomarkers or cardiac function in individuals who have suffered a cardiac event.

3 THEORETICAL FRAMEWORK

Regularly attending CR significantly improves health outcomes following a cardiac event. BACPR recommends that 'the patient should receive individual guidance and advice on active daily living together with a tailored activity and exercise plan with the collective aim to increase physical fitness, as well as overall daily energy expenditure and decrease sedentary behaviour' following a cardiac event. However, little is known regarding the effects of breaking up sitting time on cardiometabolic risk markers in this population. In healthy individuals and those with impaired metabolic health, breaking up sitting time results in favourable reductions in cardiometabolic risk markers over a single day. It can therefore be hypothesised that breaking up sitting in cardiac patients will reduce cardiometabolic risk markers and thus contribute to a reduced risk of a secondary cardiovascular event.

4 RESEARCH QUESTION/AIM(S)

1) What are the effects of breaking up sitting time on cardiometabolic risk markers and cardiac function in patients following a myocardial infarction?

4.1 Objectives

To determine whether breaking up sitting time with standing or light physical activity acutely improves cardiometabolic risk markers and cardiac function in individuals who have suffered a myocardial infarction.

4.2 Outcome

The primary outcome of this study is postprandial glucose. Other outcome measures include: (i) cardiometabolic risk markers: postprandial triglycerides, high density lipoprotein cholesterol (HDL-C), c-reactive protein, insulin, and blood pressure (ii) cardiac function: global longitudinal strain (%), stroke volume (L) and ejection fraction (%), and (iii) mood and wellbeing.

5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYSIS

Study design

A repeated measures, randomised cross over study design will be used. All data collection will take place at the Sport and Exercise Science Laboratories, University of Bedfordshire, Polhill Avenue, Bedford, UK. After a preliminary testing session, participants will complete three, 6-hour experimental conditions in a random order: 1) uninterrupted sitting; 2) sitting interrupted with standing breaks, and 3) sitting interrupted with light intensity stepping breaks. There will be a washout period of at least 72 hours between conditions, as previous research suggests that a single session of exercise can affect blood glucose levels for the following 48 hours (Mikines, et al., 1988). Participants will be randomised to order of condition using computer generated random numbers. This will assign them a trial order using block randomization with balanced block sizes. Participants will be blinded to the trial condition until they arrive on the day of their first and second experimental conditions.

Preliminary testing

Patients will first attend a preliminary testing session where they will become accustomed to light intensity stepping on the spot to the beat of a metronome and use of the Borg RPE scale. This will ensure patients are familiar with an intensity that is equivalent to an RPE of 8-11 (very light to light) that will be used in the respective experimental condition. Participants will step to different metronome paces starting at a slow pace and building up gradually every 1-2 minutes until an RPE of 8-11 is found. This imitates the intensity recommended within the warm up of CR, as recommended by BACPR. Height (cm) and weight (kg) will also be measured using a stadiometer (Harpenden 98.602, Holtain Ltd., Crymych) and digital scales

(Tanita BWB0800, Tanita Corp., Tokyo, Japan) respectively, to calculate body mass index (kg/m^2).

Experimental Protocol

Participants will be asked to refrain from any alcohol and caffeine for 24 hours prior to each visit, as well as avoid exercise for 72 hours and complete an overnight fast. This will be explained to them during the preliminary visit. To monitor this, they will be asked prior to participation per visit whether they have fasted/ when they last ate and drank.

Participants will be asked to perform an overnight fast for at least 10 hours before arrival and minimise active travel to the laboratory (e.g. use a car for travel). They will rest for 30 minutes to achieve a steady state before baseline blood pressure (two measures with 2 minutes rest between each and the average taken) and blood samples are taken. Baseline cardiac function measures (global strain, ejection fraction and systolic volume) will be measured using an echocardiogram scan, as well as an electrocardiogram (ECG) to ensure there are no electrical contraindications to the heart which would make the participant unsuitable to complete the study intervention including ST depression / elevation or any arrythmias. Baseline mood and wellbeing measures will then be assessed using questionnaires.

Following baseline measures, a standardised breakfast will be consumed (see meals section below) and participants will then commence the experimental condition. See Figure 1 for schematic of experimental conditions.

The three experimental conditions for this study are:

1) Uninterrupted sitting for 6 hours.
2) Sitting interrupted with 5 minutes of static standing every 30 minutes.
3) Sitting interrupted with 5 minutes of light intensity stepping every 30 minutes using a metronome at the intensity determined during preliminary testing. This replicates active recovery time currently performed in a phase III CR class.

A lunch meal will be provided at 12:00 during each condition. During sitting periods, participants will be able to read books, magazines or newspapers and/or watch TV, DVDs or media streaming services. Participants will be transported to the toilets and food consumption areas using a wheelchair to ensure activity is minimised and standardised between conditions.

Standardised food and water intake

Each meal will provide approximately 30% of estimated daily energy requirements. This will be calculated for each individual participant using a prediction equation based on individual's height, weight and gender. Breakfast will consist of bran flakes, whole milk, and a honey and granola bar and will consist of 54% carbohydrate, 34% fat and 12% protein. Lunch will consist of a chicken sandwich, salted crisps and jammie dodger biscuit (54% carbohydrate, 34% fat and 12% protein). The macronutrient composition of the meals are in general agreement with guidelines recommended for a balanced diet (Public Health England, 2016). Participants will be encouraged to consume their meal within 15 minutes. The time taken will be recorded in the first condition and this time will then be replicated in the latter two conditions. Water will be available for the participants ad libitum during their first experimental condition visit. This volume of intake will be recorded and the same amount provided in the following two conditions spread over the day.

Data collection

Finger prick capillary whole blood samples will be collected at baseline, 30, 60, 120, 180, 210, 240, 300 and 360 minutes throughout the conditions to allow later analysis of glucose, triglycerides, HDL-C, and insulin. Blood samples will be taken after the hand is pre-warmed in warm water for approximately 5 minutes. Blood pressure and heart rate will be measured 5 minutes before each of the blood samples are taken. Cardiac function measures and mood and wellbeing will be measured at baseline and post-condition

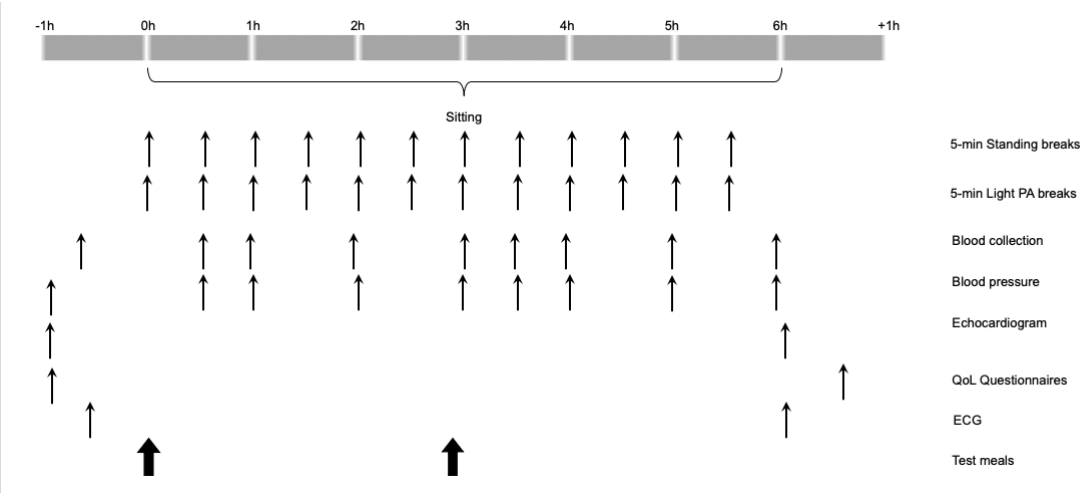


Figure 1: Schematic of experimental protocol, PA, physical activity; ECG, electrocardiogram.

Biochemical analyses

600μl of whole capillary blood will be collected using EDTA microvette tubes that will be centrifuged (Heraeus Pico 17 microcentrifuge; Thermo Scientific, Loughborough, UK) at 2000 × g for 5 min. The plasma will then be pipetted into 0.5 mL eppendorf tubes and stored at -80° for later analysis. Plasma glucose and triglyceride concentrations will be analysed via enzymatic colorimetric methods using a benchtop analyser (Pentra 400; HORIBA ABX Diagnostics, Montpellier, France). Plasma insulin concentrations will be determined using an enzyme linked immunosorbent assay technique (Mercodia, Uppsala Sweden).

Blood pressure and heart rate

Blood pressure and heart rate will be measured in an upright, seated position using an automated device (Omron M5-1 automated oscillatory device, Omron Matsusaka Co. Ltd., Matsusaka, Japan). The same arm will be used for BP measurement each time throughout the study, which will be taken on the left arm unless there is preference for the right arm due to any potential previous medical conditions. A single measure will be taken at each time point apart from baseline where two measures will be taken with a 2 minute rest between each.

Cardiac function

In a laboratory, the patient will be asked to undress from the waist up and lay on the medical couch in the left lateral decubitus position. Here, a scanning gel will be applied to the echocardiogram probe. This forms part of the echocardiogram system; Vivid 7, GE Medical, Mius Ltd., Gloucester, UK). Parasternal and apical views will be acquired (Armstrong and Ryan., 2012). Once these images are collected and stored, the gel will be removed from the probe and chest. All images will be stored anonymously, where participants will be given a participant ID number. All image analysis will be completed using Echopac software (GE Healthcare, Version 113, GE healthcare, Chicago, Illinois, United States).

LV mass, LV mass index (adjusted for height), LV end diastolic volume, LV end systolic volume, wall motion score index (WMSI), E/A ratio, relative wall thickness, and deceleration time will be measured. These measures will be used to calculate left ventricular function.

Mood and wellbeing

The Positive and Negative Affect Scale (PANAS) questionnaire (Watson et al., 1988) will be used to assess current mood and subjective wellbeing measured using the National Wellbeing Measurement. These questionnaires will be completed at baseline and immediately after

cardiac function measures post-condition. There is a significant correlation post cardiac event and poor mental health (Chadda, et al., 2016). This questionnaire will therefore measure whether breaking up sitting time regularly within this population will improve mental health measures. PANAS is a valid questionnaire, which can be modified to measure changes in mood across a day, without losing its validity (Watson, et al., 1988). If incidental findings of anxiety or depression occur, the GP shall be informed via a letter sent directly to them.

Data analyses

Statistical analyses will be conducted using SPSS Version 23 (IBM, Armonk, NY, USA). Postprandial glucose, insulin, triglycerides, HDL-C, SBP and DBP iAUC will be calculated for each condition using the trapezoidal rule. Mean arterial blood pressure will be calculated as: $MAP \cong P_{Diastolic\ blood\ pressure} + \frac{1}{3}(P_{systolic\ blood\ pressure} - P_{diastolic\ blood\ pressure})$. Normality of the data will be checked using quantile-quantile plots. Linear mixed models will be used to compare the dependent variables between conditions. Fixed factors for each model will be condition and fasting outcome variable values (as covariates) and participants will be entered as a random factor. Post-hoc analyses will be conducted use the Sidak adjustment if a significant main effect of condition is present. Cohen's d effect sizes will be calculated to describe the magnitude of differences between conditions. Data will be presented as a mean (95% CI). Significance will be set at $p<0.05$.

6 STUDY SETTING

All testing will take place at the University of Bedfordshire Sport and Exercise Science Laboratories.

7 SAMPLE AND RECRUITMENT

7.1 Eligibility Criteria

7.1.1 Inclusion criteria

- Patients post myocardial infarction (ST wave elevated MI or Non-ST wave elevated MI) within the past three months (confirmed by elevated blood biomarkers or electrocardiographic changes), in which the procedure/ recovery uncomplicated and are therefore classified as low risk.
- Aged 40 years or above.
- Any ethnicity.
- Individuals with diet controlled type 2 diabetes mellitus

7.1.2 Exclusion criteria

- Previous MI
- Under 40 years of age.
- Unable to provide valid informed consent (lack of mental capacity).
- Not had a cardiac event diagnosed within the past three months.
- Existing comorbidities including cancer, chronic kidney disease and gastro-oesophageal diseases.
- Unstable coronary disease.
- Diagnosed diabetes and use of medication.
- Disease or conditions with a prognosis of less than 6 months to end of life (palliative care). Any known blood borne disease.
- Unable to stand and engage in light-intensity stepping.

7.2 Sampling

7.2.1 Size of sample

An estimated sample size was calculated using G* Power (version 3.1.9.4). Based on previous data (Bailey, et al., 2019), it was estimated that 18 participants would be needed to detect a medium effect size (f=0.5) difference in iAUC postprandial glucose between conditions with 95% power at an alpha level of 5% and within-person correlation of 0.5. To allow for 20% drop out, 23 participants will be recruited. If drop out occurs and recruitment is lower than 18 , participants will be replaced to ensure minimum recruitment is met. This decision will be pragmatic in accordance with study timeline.

7.2.2 Sampling technique

Eligible patients will be approached during their phase 2 CR consultation with the CR multidisciplinary team. Convenience sampling will be used to ensure sufficient recruitment to the study.

7.3 Recruitment

7.3.1 Sample identification

Participants will be identified by a member of the university research team who will regularly attend CR initial assessment clinics. This member is also employed at Bedford Hospital as a Cardiac Rehabilitation Exercise Specialist. They will have access to the clinic list and medical notes prior to the consultation, where they can be screened to check who may be eligible for the study. This is usual practice as part of the role of a Cardiac Rehabilitation Exercise Specialist. All members of the research team involved in recruitment will have an NIHR research passport and will have completed secondary GCP (Cardiac Rehabilitation Exercise Specialist). Eligible patients will be approached by the Cardiac Rehabilitation Exercise Specialist to ask if they would be interested in volunteering to take part in the study.

Participants will be approached after their initial CR appointment by a member of the research team to invite them to take part in the study. An introduction to the study will be given and the patient will be given a participant information sheet (PIS) to take away. A consent to contact form will be completed that allows the research team to call the patient to discuss the study further and explore whether they are interested in participating. It is optional and refusal to do so does not in any way affect their usual standard of care. If they complete a consent to contact form, the patient will be given at least 24 hours to read the PIS and discuss with friends and family, to carefully consider their participation in the study.

7.3.2 Consent

Only patients with capacity to consent will be considered eligible for the study. If the patient would then like to participate in the study, an informed consent form will be given for them to complete and sign. Should a patient lose capacity during the follow up period, they will be withdrawn from the study. Identifiable data or blood samples already collected with consent would be retained and potentially used in the study. No further data or samples would be collected or any other research procedures carried out.

For an individual to have capacity to consent they will: understand the purpose and nature of the research; understand what the research involves, its benefits (or lack of benefits), risks and burdens; understand the alternatives to taking part; be able to retain the information long enough to make an effective decision; be able to make a free choice; be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity).

8 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Assessment and management of risk

Physical Activity

As patients will be asked to do light intensity physical activity, there is a very small risk of injury and falls. However, risks will be kept very minimal by asking the patient to complete a health questionnaire to check for any contraindications. If any symptoms become evident during the study, participants will be asked to stop straight away and monitored for an appropriate amount of time. There will also always be a first aider available on site.

Blood Collection

There is a small risk of bruising associated with blood collection. To reduce this, research members will be trained in the appropriate blood collection technique, which adhere to published guidelines.

There is a very small risk of contamination from blood sample collection. However, these risks will be minimized by using protective equipment, disinfecting all re-useable equipment and screening all participants with a health questionnaire before they take part in the study. Individuals will be asked not to take part in the study if they have a blood borne disease or virus.

Further heart abnormality findings

An ECG will be carried out by a suitably trained professional prior to each condition taking place. If any changes to the electrical activity of the heart are observed, the study will not be carried out and the participant will be advised to get in contact with their GP or an ambulance will be called, depending on what the findings are.

Echocardiogram scanning

There is a small risk of a skin reaction to the gel used during scan. However, it is a hypo-allergenic gel. To minimise this risk further, a small patch test will be carried out prior to the study taking place. If there is any redness around the area applied, the scan will not go ahead. Further to this, there may be slight discomfort to the participant when the scan is taking place, through either a cold gel, slight pressing on the chest or being unclothed on their top half. It will be highlighted to them that it is important to inform the researcher of any discomfort and that they are free to stop the study at any time. If any areas of concern are highlighted during the echocardiogram, the participant's GP will be informed by writing a letter to them.

If an adverse event occurs, there is a qualified advanced first aider (also trained in AED and gas) on site in the laboratory at all times. There is access to first aid equipment (first aid box, AED, oxygen) and a telephone, where an ambulance would be called. The GP will be notified of any event that occurs during data collection. Likewise, if there are any incidental findings regarding the results obtained during the study, the GP will be notified via a letter detailing the findings.

8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from the NHS REC.

- Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.
- All correspondence with the REC will be retained.
- It is the Chief Investigator's responsibility to produce the annual reports as required. The Chief Investigator will notify the REC of the end of the study.
- An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.
- If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.
- Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC.

Regulatory Review & Compliance

Before patients are enrolled into the study, the Chief Investigator will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance. For any amendment to the study, the Chief Investigator, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

Amendments

If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor will submit a valid notice of amendment to the REC for consideration. The REC will provide a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the REC.

Amendments will also to be notified to the *national coordinating function of the UK* country where the lead NHS R&D office is based and communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site.

In all instances the protocol will describe:

- The process for making amendments.
- Who will be responsible for the decision to amend the protocol and for deciding whether an amendment is substantial or non-substantial?
- How substantive changes will be communicated to relevant stakeholders (e.g., REC, R&D, regulatory agencies).
- How the amendment history will be tracked to identify the most recent protocol version.

8.3 Peer review

As this study forms part of a PhD project, it has been reviewed by two academic supervisors.

8.4 Patient & Public Involvement

Cardiac Rehabilitation Team at Bedford Hospital

Regular meetings will be held between the Bedford Hospital Cardiac Rehabilitation team and the study investigators to discuss how to conduct the study in terms of participant recruitment, data collection and dissemination.

Patient and Public Involvement

A PPI focus group study session has been held with post MI patients to discuss the study design and coordination. This helped the research team to understand any difficulties with

recruitment that they may face, as well as how best to conduct the study. They have also been shown patient facing documents to ensure they are suitably aimed at the target population.

8.5 Protocol compliance

Accidental protocol deviations can happen at any time. If they are to occur, they must be adequately documented and reported to the Chief Investigator and Sponsor immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach. Here, they will also be reported to the NHS REC.

8.6 Data protection and patient confidentiality

All investigators and study site staff will comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles, to ensure that patient confidentiality is maintained at all times.

Personal information on source documentation will be filed in a locked cabinet, with only the core research members allowed access. Upon registration to the study, participants will be given a unique participant ID number, which will henceforth be used in all data collection within the study. This will be determined using a number system (Move-01, etc.). A confidential log will be kept by the research team to identify participants with their anonymous ID numbers, which will be encrypted on a secure computer. All other electronic documentation will also be encrypted. Only direct members of the research team will have access to the data, and will be listed on the study's delegation log. Where data is transmitted to sponsors, if necessary, it will only be identifiable by its participant ID number, thus not becoming patient identifiable at any time.

Upon completion of the study, data will be stored for a minimum of 5 years. The data custodian for the Project is Dr Joanna Richards, Lecturer for Clinical Physiology.

8.7 Indemnity

The University of Bedfordshire holds insurance and will provide indemnity to cover relative liabilities associated to this research project. Please see the University of Bedfordshire 'Certificate of Employers Liability Insurance' and 'Professional Indemnity Certificate', which includes insurance cover for research.

8.8 Access to the final study dataset

All members of the research team will have access to the final study dataset. Following publication of the study, access may be available for secondary analysis of the anonymized dataset on reasonable request to the Chief Investigator, which would not be patient identifiable. All patient documentation will reflect the future use of these data in research if necessary.

9 DISSEMINIATION POLICY

9.1 Dissemination policy

All data arising from the study will be property of the University of Bedfordshire. On completion of the study, the data will be analysed and a final study report prepared. The full study report will be accessible by all, as it will be made publically available. The chief investigator will have the right to publish the final report. Participants will be notified of the outcome of this study by receiving a summary of its findings. Overall, a manuscript will be written for submission to a peer reviewed journal.

9.2 Authorship eligibility guidelines and any intended use of professional writers

Authorship will be based on the following 4 criteria, in accordance with the ICMJE:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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