Hull University Teaching Hospitals NHS Trust

Exercise in patients with a total Coronary Occlusion – EChO - 247135

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Glossary

CTO – Chronic total Occlusion

O_2 – Oxygen

CO_2 – Carbon Dioxide

VO_2 – Oxygen Uptake

VCO_2 – Carbon Dioxide Output

CHD – Coronary Heart Disease

PCI – Percutaneous Coronary Intervention

HRR – Heart Rate Reserve

CV – Cardiovascular

O_2/HR – Oxygen pulse

$\Delta VO_2/\Delta WR$ – The change in oxygen uptake versus the change in work rate

CPET – Cardiopulmonary exercise test

SV – Stroke volume

Q – Cardiac output

a-vO_2 – Arteriovenous oxygen difference

ATP – Adenosine triphosphate

HR – Heart rate

ECG – Electrocardiograph

VAT – Ventilatory anaerobic threshold

Background and Rationale

Coronary heart disease (CHD) is the biggest cause of death in the United Kingdom (UK) accounting for approximately 69,000 deaths each year. The annual incidence of CHD is estimated to be 490,000 (Miller 2008, Townsend et al. 2014). Exercise training is indicated in patients with coronary heart disease (CHD), including those with exercise-induced myocardial ischaemia. Benefits include the attenuation of disease progression, symptom improvement, increased exercise tolerance (Hambrecht et al. 2004, Niebauer et al. 1997) and, improved quality of life (Belardinelli et al. 2001). However, there is a paucity of data on the effects of exercise training in patients with a total chronic occlusion (CTO) of a major coronary artery.

A CTO is identified in up to 50% of patients found to have significant coronary artery disease on coronary angiography (Christofferson et al. 2005). The presence of a CTO has an impact on the subsequent treatment of the patient with the majority either managed medically or referred for bypass graft surgery. The reasoning for this relates to the challenge of performing percutaneous coronary intervention (PCI). Recent data from the UK National database indicates that of 14,439 procedures, the success rate of CTO PCI was only 70.6% - considerably lower than if the vessel is not chronically occluded (George et al. 2014).

It is important to appreciate that the vessel distal to the occluded segment is filled either antegradely or retrogradely via collaterals. However, these collaterals are not sufficient to prevent ischemia to the myocardium (Werner et al. 2006). During activity, patients may experience symptomatic or asymptomatic exercise-induced myocardial dysfunction, reduced exercise tolerance and limited functional independence.

The perceived inability of patients to safely and effectively sustain a programme of physical activity may lead to a further decline in quality of life and accelerated disease progression. This is likely to incur further primary and secondary care costs. However, exercise therapy could potentially help the development of the collateral blood supply (Möbius-Winkler et al. 2016). This may not only increase the ischemic threshold, but might also help to facilitate an increase in the success rate of PCI either antegradely (via micro-channels) or retrogradely whereby the collaterals may be traversed to

facilitate recanalisation. Specialist exercise prescription techniques in this population may therefore aid the management of this condition.

Summary of Proposed Research

A CTO is defined as a full coronary artery occlusion with a thrombolysis in myocardial infarction (TIMI) flow of zero, for more than three months (Di Mario et al. 2007). Despite exercise training forming the 'corner stone' of any long-term treatment of patients with CHD, there is no specific training advice for patients with a CTO. Current exercise training guidance offered by the ACPICR (2015) recommends training intensities of 40-70% heart rate reserve (HRR), or intensities below the ischaemic threshold for those with known myocardial ischaemia. However, not only do patients with a CTO often suffer silent ischaemia making the latter training guideline inadequate, sustained cardiovascular (CV) exercise below an ischaemic threshold may still lead to patients becoming symptomatic owing to VO_2 drift, subsequent heart rate (HR compensation) and, increased myocardial workload (Mezzani et al. 2013, Ellestad 1996, Zafrir et al. 1999). Given current cardiac rehabilitation guidelines indicate that increasing total CV exercise time should be a key objective, CTO patients may be receiving suboptimal training prescriptions.

Although the safety of exercise training during periods of ST-segments depression (1 to 3mm) over periods of 12 to 50 minutes has been reported (Noël et al. 2007), prolonged periods of myocardial ischaemia may increase the risk of arrhythmias (Kléber and Rudy 2004). Moreover, frequent episodes of angina are likely to evoke patient anxiety (Arnold et al. 2009). A method of reliably avoiding angina or arrhythmia during exercise training would be advantageous.

Inflections in the oxygen pulse [O_2/HR]) or, inflections to the 'normal' linear increase in VO_2 with work rates ($\Delta VO_2/\Delta WR$) observed during maximal cardiopulmonary exercise testing (CPET) indicate the onset of myocardial ischaemia (Belardinelli et al., 2003). These changes (on ramp-based exercise testing protocols) are reported prior to the development of angina symptoms or, ST-segment depression (265 ± 33 seconds). Exercise intensities corresponding to this work rate may be a safe and

effective threshold to base exercise training in patients with a CTO. However, no investigation has reported the variability in the occurrence of the O_2/HR and, $\Delta O_2/\Delta WR$ inflection, nor has any visual verification that exercise-induced myocardial ischaemia occurs at this point has been provided. In addition, no study has investigated whether sustained exercise prescribed at intensities based on these phenomena is feasible in this cohort. The purpose of this investigation is therefore to determine the variability in the onset of the O_2/HR and, $\Delta O_2/\Delta WR$ inflection and, to determine the feasibility and safety of exercise prescribed at intensities corresponding to O_2/HR and $\Delta O_2/\Delta WR$ inflection points.

Physiological Principles

O_2/HR is an indirect measure of stroke volume (SV) calculated from a modification of the Fick equation. The principle component of VO_2 is cardiac output (Q), hence an estimation of SV may be made by dividing VO_2 by HR (unit: ml O_2 per beat). O_2/HR therefore, is the product of SV and a-vO_2 difference (Whipp, Higgenbotham and Cobb 1996). Because myocardial ischaemia has a profound deleterious effect on SV during exercise, changes in the O_2/HR can be used to diagnose suspected exercise-induced myocardial ischaemia and flow limiting CHD (Belardinelli et al. 2003, Chaudhry et al. 2009, Wasserman et al. 2011).

In healthy populations, incremental CPET elicits a linear O_2/HR response, however, in CHD a spontaneous inflection of this response may be observed. Coronary stenosis may inhibit myocardial O_2 supply to the point where ATP re-synthesis is impaired and myocardial contractions become dyssynchronous. Subsequent myocardial wall motion abnormalities cause a reduction in SV causing a compensatory HR increase to sustain Q. HR compensation is unlikely to fully normalise VO_2. The result of increased HR is the compounding of an already inadequate O_2 supply by increasing myocardial work and, reducing diastolic and coronary artery filling times (Ellestad 1996, Chaudhry et al. 2009, Zafrir et al. 1999). The point at which a HR increase coincides with a spontaneous, premature flattening or inflection of O_2/HR (Figure 1A) is thought to be indicative of exercise-induced myocardial ischaemia (Belardinelli et

al., 2003). During ramp-based exercise testing, identification of an ischaemic threshold may also be observed to greater effect by combining O_2/HR with the VO_2 versus work rate slope ($\Delta VO_2/\Delta WR$). In healthy individuals, a linear increase in $\Delta VO_2/\Delta WR$ of ~10 $ml \cdot min^{-1} \cdot watt^{-1}$ is maintained until peak exercise where normal limitation to exercise performance may cause a plateau. A uniform flattening of this relationship (<10 $ml \cdot min^{-1} \cdot watt^{-1}$) is considered indicative of global reduction in CV efficiency and is often seen in patients with chronic heart failure (Wasserman et al., 2011). In CHD however, the 10 $ml \cdot min^{-1} \cdot watt^{-1}$ relationship may be maintained until the onset of myocardial ischaemia which causes an abrupt decline in the rate of VO_2 increase (Figure 1B). This may manifest as an objective break-point in the $\Delta VO_2/\Delta WR$ slope.

Myocardial wall-motion abnormalities and a subsequent reduction in SV are likely to occur prior to ECG changes and symptoms of angina (Nesto and Kowalchuk, 1987). Therefore inflections in the $\Delta VO_2/\Delta WR$ slope and O_2/HR relationship may be regarded as more sensitive markers of ischaemia. Indeed, (Belardinelli et al. 2003) reported on average, that this inflection occurred 265 ± 33 seconds prior to a 2mm ST segment depression.

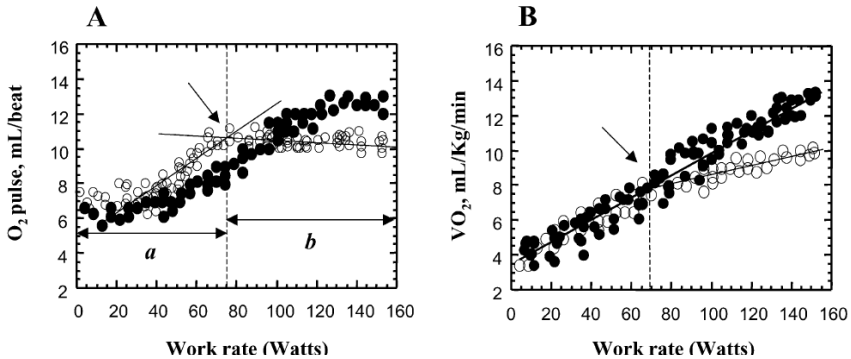

Figure 1 – Reproduced from Belardinelli et al. (2003). Panel A and B show the oxygen pulse (O_2/HR) and $\Delta VO_2/\Delta WR$ of a healthy patient (closed circles) and a patient with exercise-induced myocardial ischaemia (open circles). Under normal circumstances the O_2/HR and $\Delta VO_2/\Delta WR$ increase until peak exercise where a brief plateau occurs reflecting natural limitation to VO_2. In patients with exercise-induced myocardial ischaemia, O_2/HR and $\Delta VO_2/\Delta WR$ inflect at the point where left ventricular function is compromised.

Objectives:

- To assess the intra-patient variability in the occurrence of the O_2/HR and, $\Delta O_2/\Delta WR$ inflection in patients with a CTO during an individualised maximal CPET.

- To verify that the O_2/HR and, $\Delta O_2/\Delta WR$ inflection indicates the onset of exercise induced myocardial dysfunction by visual confirmation of its occurrence using stress-echocardiography

- To examine the safety and feasibility of sustained exercise prescribed at an intensity equal to the O_2/HR and, $\Delta O_2/\Delta WR$ inflection in patients with a CTO

Hypotheses:

- Primary: The variability in the onset of O_2/HR and, $\Delta O_2/\Delta WR$ inflection will be low (Intra-class correlation >0.75) when defined as 'Wattage at inflection occurrence'.

- Secondary: Sustained exercise at the O_2/HR and/or, $\Delta O_2/\Delta WR$ inflection will elicit clinically-significant myocardial wall motion abnormalities observed using echocardiography but will not result in ST-segment depression > 2mm, or other ECG changes and symptoms indicative of angina.

- Secondary: Sustained exercise at an intensity equal to the O_2/HR and, $\Delta O_2/\Delta WR$ inflection will not result in serious adverse event requiring medical intervention.

Study Design

Figure 2 outlines the study protocol. The study is a single centre, pilot study recruiting patients with single vessel disease with a complete chronic occlusion. Consecutive patients will either be identified at the time of diagnostic coronary angiography, or retrospectively from the dedicated departmental database which contains information on every patient who undergoes angiography / angioplasty by their usual clinical care team. Patients may be included if they are either 1) awaiting attempted angioplasty or 2) are being managed with medical therapy. The department performs approximately 35-40 CTO procedures per year in patients with single vessel disease who would be potentially suitable for inclusion into the study. Approximately 5-10 patients per year have single vessel disease and a CTO, and have an unsuccessful PCI procedure. These patients are maintained on medical therapy and can be identified from the departmental database. All patients will have good resting left ventricular function as evidenced by either echocardiography or left ventriculography. Patients with multi-vessel disease will be excluded. Wherever possible, patients will be stabilised on optimal medical therapy so that adjustments to this therapy can be avoided during the study period.

Twelve consecutive patients fitting the inclusion criteria will be approached at the time of coronary angiography or will receive a telephone call from a member of their usual clinical care team inviting them to take part in the study. A patient information leaflet (PIL) will be provided or sent through the post if the patient is interested in participating. Approximately one week later, after the patient has had time to consider their involvement (>24 hours later) they will be followed up by their usual clinical care team to ask if they would like to proceed with study participation, and if they consent to be contacted by the research team. Once agreed, a patient will be contacted by the research team to answer any questions they may have about the protocol and be invited for a baseline assessment (visit 1) where informed consent will be obtained.

Investigations at visit 1 will include; a brief medical assessment involving the collection of resting pulse rate, blood pressure, height, weight, resting 12 lead ECG, resting echocardiogram, and resting blood sample (full blood count and biochemical profile,

glucose and troponin T). Following these measures, the patient will complete a symptom limited maximal CPET, followed by a repeat blood test for troponin T.

Patients will then attend a second visit (visit 2) after a minimum of 72 hours up to a maximum of two weeks later. This will include all measures from visit 1, minus the pre and post exercise blood samples and resting echocardiogram. The repeated maximal CPET will follow the same protocol as visit 1. Data from the maximal CPET at visit 1 and 2 will be analysed to determine the work rate at the onset of O_2/HR and/or, $\Delta O_2/\Delta$WR inflection. If an inflection cannot be identified, patients will be withdrawn from the study. This will be recorded in any subsequent publications.

A third visit (visit 3) will take place a minimum of 72 hours up to a maximum of 2 weeks following visit 2. Patients will receive; a brief medical assessment involving the collection of resting pulse rate, blood pressure, height, weight, resting 12 lead ECG, resting echocardiogram, and resting blood sample. A *sub-maximal* CPET at an intensity corresponding to the O_2/HR and/or, $\Delta O_2/\Delta$WR inflection [minus two thirds of the CPET ramp rate] (Whipp et al. 1981) lasting 20 minutes will then be conducted. If there is disagreement between the work rate that O_2/HR and $\Delta O_2/\Delta$WR inflection occurs, a workload corresponding to the difference between the two will be prescribed. During the final 5 minutes of the CPET the cycle ergometer will be placed in the supine position and a cardiac sonographer will complete a stress echocardiograph to ensure continuous exercise at this work rate does not elicit adverse events. After the CPET is complete and the patient has rested for 6 minutes on the bike, a final blood sample will be taken for comparison.

Belardinelli et al (2003) indicate that the patients who exhibit O_2/HR and/or, $\Delta O_2/\Delta$WR inflections are most likely to do so below the ventilatory anaerobic threshold (VAT). Because work rates below the VAT produce predictable changes in VO_2, the influence of VO_2 drift is unlikely to lead to an internal work rate higher than that documented during maximal CPET (Mezzani et al. 2013).

Following the final blood sample patients will be offered light refreshments.

Inclusion criteria

- Single vessel disease with a chronic total occlusion of the right coronary artery, left anterior descending artery, or left circumflex artery, as identified on coronary angiography performed within the preceding 24 months.
- Willingness to undertake maximal cardiopulmonary exercise test
- Resting systolic blood pressure <180mmHg
- Resting Diastolic blood pressure <100mmHg
- Aged >18yrs
- Normal resting left ventricular function
- Able to provide written informed consent

Exclusion criteria

- Significant proximal left main stem stenosis.
- Multi-vessel disease (defined as a diameter stenosis of >50% in another major epicardial coronary vessel)
- Absence of exercise-induced ischaemia evidenced by O_2/HR or, ΔVO_2/ ΔWR inflection at visit 1 and 2
- O_2/HR inflection or, ΔVO_2/ ΔWR inflection at a respiratory exchange ratio >1.05
- Change in cardiac medications within previous two weeks
- Unstable angina
- Myocardial infarction within the preceding 6 weeks
- Canadian classification system for angina class IV
- Chronic heart failure
- Significant valvular pathology
- Resting ejection fraction <40%
- Severe orthopaedic limitations
- Past history of Complex arrhythmias
- Atrial fibrillation
- Severe COPD

- Symptoms of intermittent claudication
- Unable to provide written informed consent
- Previous permanent pacemaker implant
- Use of short-term GTN within 30 minutes of exercise testing

Sample Size

The aim of this study is to investigate the feasibility and safety of prescribing exercise at work rates corresponding to the O_2/HR and/or, $\Delta O_2/\Delta WR$ inflection in patients with a CTO. There is currently no published literature detailing the use of this technique and therefore, this investigation should be considered a pilot study. Julious (2005) states that the minimum number of participants for a clinical pilot study is *n*=12. We will therefore recruit *n*=12 participants into this cohort study. Because the focus of this study is on determining agreement rather than determining statistical significance, a small sample size will not limit our ability to investigate our primary outcome.

Study procedures

Symptom Limited Maximal Cardiopulmonary Exercise Testing (Cycle)

- Breath-by-breath gas analysis
- Continuous ECG monitoring
- Three minute unloaded cycling phase at 40-60 rpm
- Personalised ramp protocol using cycle ergometer (60rpm)
- Follows (American Thoracic Society/American College of Chest Physicians 2003) guidelines
- Rating of perceived exertion (Borg 1982)

Determination of O_2/HR and $\Delta O_2/\Delta$WR inflection

Following symptom limited maximal CPET, breath-by-breath data will be exported for offline analysis (15 second average). The instantaneous ration of oxygen uptake to heart rate (O_2/HR) will be plotted against work rate (WR). A plateau or reduction in the (O_2/HR) despite increasing work rate will be considered indicative of myocardial ischaemia. $\Delta VO_2/\Delta$WR slope will also be calculated as peak VO_2-unloaded VO_2/T-0.75×S, where peak VO_2 is VO_2 at peak exercise, T is the time of incremental exercise, S is the slope of work rate increment in watts per minute. A $\Delta VO_2/\Delta$WR slope will be deemed abnormal if an inflection in VO_2 is observed with respect to WR despite evidence of a normal slope (~10 $ml \cdot min^{-1} \cdot watt^{-1}$) from the onset of exercise start to the inflection point, and a flattened slope. An inflection in the O_2/HR or $\Delta VO_2/\Delta$WR slope will not be deemed abnormal if it occurs during the last 30 seconds of exercise as this can result from normal physiological limitations to exercise (VO_2 plateau). This protocol reflects the seminal work by (Belardinelli et al. 2003).

Fixed Workload Cardiopulmonary Exercise Testing (Cycle)

- Breath-by-breath gas analysis
- Three minute unloaded cycling phase at 40-60 rpm
- 20 minutes of exercise at work load corresponding to O_2/HR and/or, $\Delta O_2/\Delta$WR inflection
- Continuous ECG monitoring
- Rating of perceived exertion (Borg 1982)
- Stress-echo follows BSE guidelines
- Termination of exercise upon symptoms or ECG changes indicative of myocardial ischaemia

Venepuncture

- Taken from the anti-cubital vein or other routine venous access point
- Bloods collected in EDTA, SST tubes
- Centrifugation

Resting Echocardiogram

- Resting ejection fraction, myocardial dimensions and, end-systolic and diastolic volumes
- Exclude significant valvular pathology
- Follows BSE guidelines

Safety and Feasibility

In addition to data on agreement, symptoms of angina, development of ECG changes indicative of myocardial ischaemia will be recorded. Any patients unable or unwilling to complete the protocol will also be recorded.
In the event that any participant complains of chest pains either before or during the test that test will be ceased.

Whilst cardiopulmonary exercise testing does bring with it an increased chance of adverse events the likelihood of this happening is still relatively low. Indeed previous research has suggested these events occur in less than 0.16% of tests (Skalski et al., 2012).
Whilst there is no research to date that directly assesses the safety of CPET in CTO patients, the afore mentioned study by Skalski et al (2012) did recruit a cohort comprising 5060 high-risk cardiac patients. As per the clinical diagnosis pathway most of the patients recruited to the study will have already performed exercise stress testing, therefore in the clinical opinion of the principle investigator (Dr Angela Hoye)

there are no clinical concerns (e.g. risk of participation) associated with the protocol. To mitigate the chances of adverse events during this study all exercise sessions will be conducted at the cardiology research department of Castle Hill Hospital. Participants will be encouraged to exercise to the limit of their capacity in an environment where they are closely monitored and immediate medical care is on hand. This could provide participants intimidated by or reluctant to exercise with the chance to test their physical capabilities in a safe and secure manner, thus alleviating some of the stress and anxiety caused by their condition.

Statistical Analysis

If statistical assumptions are not violated, data analysis will be conducted using intra-class correlations, coefficient of variation and, Bland-Altman plots detailing mean bias and limits of agreement. Because this study is a pilot study, utilisation of p-values will be minimal. Number of dropouts, ECG abnormalities and any adverse events will be reported descriptively.

Study flow chart

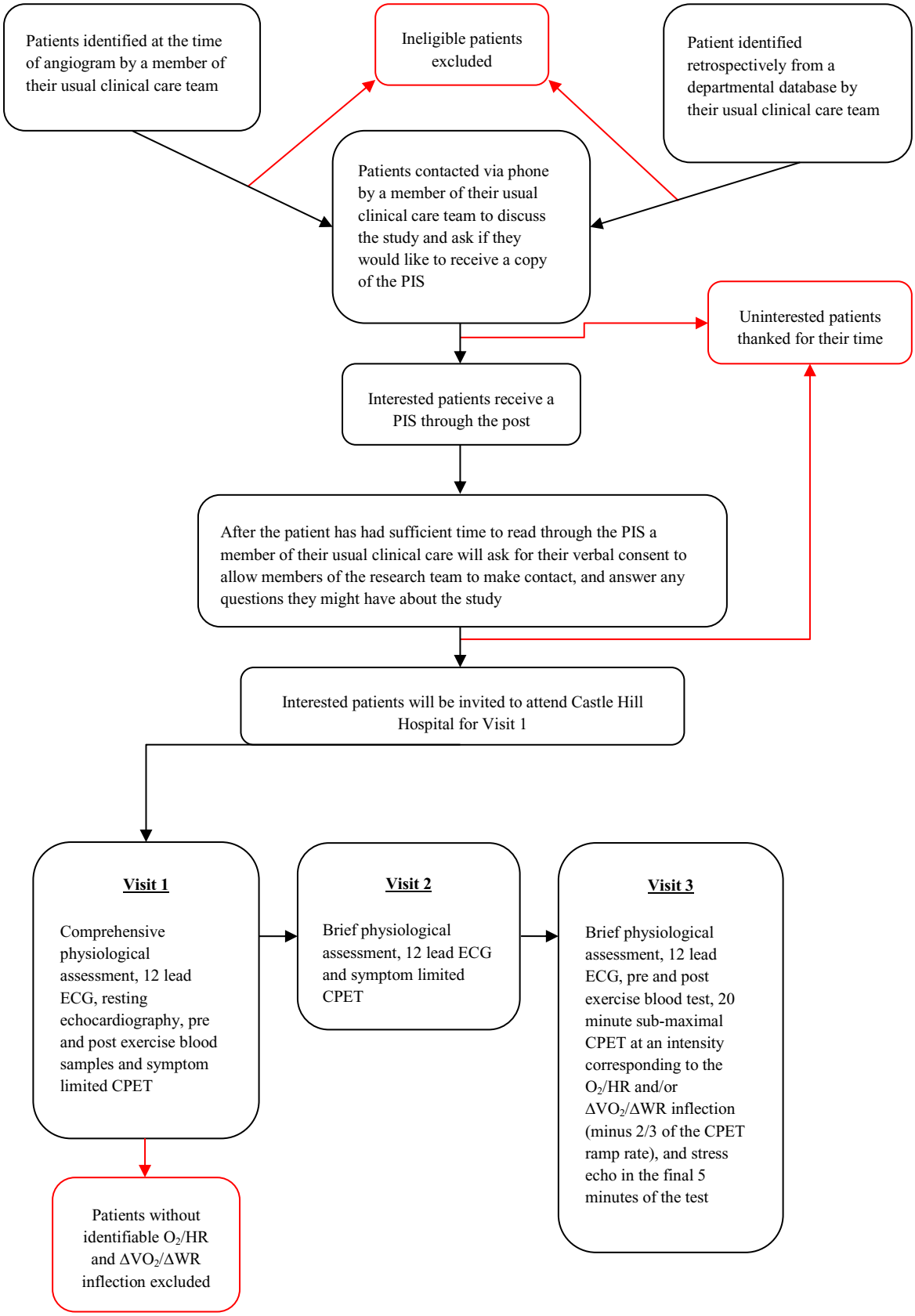

Figure 2 – Study flow chart.

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