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A randomised trial comparing the effect of exercise training and weight loss on microvascular function in coronary artery disease ☆,☆☆

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ABSTRACT

Background: Coronary microvascular function is associated with outcome and is reduced in coronary artery disease (CAD) and obesity. We compared the effect of aerobic interval training (AIT) and weight loss on coronary flow reserve (CFR) and peripheral vascular function in revascularised obese CAD patients.

Methods and results: Seventy non-diabetic patients (BMI 28–40 kg×m^{-2}, age 45–75 years) were randomised to 12 weeks' AIT (three weekly sessions lasting 38 min with ≈16 min at 85–90% of VO_2peak) or low energy diet (LED, 800–1000 kcal/day). Per protocol adherence was defined by training-attendance ≥60% and weight loss ≥5%, respectively. CFR was assessed by Doppler echocardiography of the LAD. Peripheral vascular function was assessed by arterial tonometry as reactive hyperaemia index (RHI) and augmentation index. Most participants had impaired CFR with a mean CFR of 2.38 (SD 0.59). Twenty-six AIT and 24 LED participants completed the study per protocol with valid CFR measurements. AIT resulted in a 10.4% improvement in VO_2peak and LED in a 10.6% weight loss (between group differences both $P < 0.001$). CFR increased by 0.26 (95%CI 0.04;0.48) after AIT and by 0.39 (95%CI 0.13;0.65) after LED without significant between-group difference (−0.13 (95%CI −0.45;0.20)). RHI and augmentation index remained unchanged after both interventions ($P > 0.50$). Intention-to-treat analyses showed similar results.

Conclusions: 12 weeks' AIT and LED increased CFR by comparable magnitude; thus both interventions might impact prognosis of CAD through improvement of coronary microvascular function.

Clinical Trial Registration: URL: http://www.clinicaltrials.gov. Unique identifier: NCT01724567.

1. Introduction

Coronary microvascular function is increasingly being recognised as an important pathophysiologic and prognostic factor in cardiovascular disorders [1–3]. Microvascular function is reduced in coronary artery disease (CAD), even in territories without prior coronary artery stenosis [4], and impaired microvascular function carries a poor prognosis [2,3,5]. Coronary microvascular dysfunction is also associated with risk factors related to a sedentary lifestyle; such as obesity [6–8], hypertension [9,10], dyslipidaemia [11,12], insulin resistance [8,13–15], and reduced exercise capacity [16,17].

Both physical inactivity and obesity are key issues in secondary prevention of CAD and there remain large unmet needs. In the recent EUROASPIRE III survey, comprising ≈14,000 CAD patients from 22 European countries; >80% of patients were overweight or obese (BMI > 25 kg×m^{-2}) and of them, only 37% performed physical activity regularly [18]. In spite of this, only a few small randomised studies have assessed the effect of lifestyle interventions on coronary microvascular function in CAD. These have all been on exercise training and have shown improvement in microvascular function measured as increased coronary flow reserve (CFR) [19–21]. In one non-randomised study of sedentary obese women, a combination of physical activity and weight loss also resulted in increased CFR [7]. The effect of isolated weight loss on coronary microvascular function in CAD has not been studied previously.

Thus both increased fitness and reduced fatness might be able to improve coronary microvascular function, but the effects have yet to be

Abbreviations: AIT, aerobic interval training; AIx, augmentation index; AI@75, augmentation index normalised for heart rate; BP, blood pressure; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; CFR, coronary flow reserve; CFV, coronary flow velocity; FFM, fat-free mass; FMD, flow-mediated dilation; LAD, left anterior descending artery; LED, low energy diet; LVEF, left ventricular ejection fraction; PAT, peripheral arterial tonometry; PWA, pulse wave amplitude; RHI, reactive hyperaemia index; RPP, rate-pressure product.

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compared. This study (the "CUT-IT" trial) was designed to compare aerobic interval training (AIT) with a considerable weight loss (≥5%) obtained through a low energy diet (LED) in obese CAD patients with CFR as the primary outcome [22]. We also assessed the concomitant effect on peripheral vascular function.

2. Methods

2.1. Study design

Study design of "CUT-IT" was previously described in detail [22]. In summary, eligibility criteria were a diagnosis of CAD with the most recent cardiovascular event at least 6 months prior to inclusion, body mass index (BMI) 28–40 kg×m^{-2}, age 45–75 years, left ventricular ejection fraction (LVEF) >35% and no diabetes. Seventy participants were randomised (1:1) to either 12 weeks' supervised AIT (three weekly sessions lasting 38 min with 16 minutes' exercise at 85–90% of VO_2peak) or weight loss through 8–10 weeks' LED (800–1000 kcal×day^{-1}, Cambridge Weight Plan, Northants, UK) followed by a weight maintenance diet (Fig. 1) [22]. Per protocol adherence to intervention was a priori defined as: a weight loss of ≥5% in the LED group, and training attendance of ≥60% overall and ≥50% in the last two weeks of the intervention in the AIT group. The aim of this study was a direct comparison of weight loss and exercise training and therefore the main results are the per protocol analyses. All participants examined at 12-weeks entered the intention-to-treat analyses. The study adhered to the Helsinki declaration, and was approved by the ethics committee of the Capital Region of Denmark (H-4-2010-146).

2.2. Body composition and peak aerobic capacity (VO_2peak)

As previously described, body fat mass and fat free mass (FFM) were estimated by whole body dual X-ray absorptiometry, and VO_2peak was measured using a bicycle ergometer and breath-by-breath gas exchange measurements [23]. In order to account for changes in body composition VO_2peak was expressed as mL×(kg FFM)$^{-2/3}$×min^{-1}. In order to account for sex-related differences in body composition, sex-adjusted body fat percentage was used as measure of adiposity in baseline regressions.

2.3. Coronary flow reserve (CFR)

CFR was measured by the same experienced physician (RHO) using an S6 transducer and Vivid E9 (GE Healthcare, Horten, Norway) as previously described [16]. LAD was visualised by colour Doppler along the anterior interventricular sulcus, distally (modified apical 5- or 2-chamber view) or alternatively mid-distally (modified low short-axis view). Coronary flow velocity (CFV) was measured as the peak diastolic flow using pulsed-wave Doppler at rest and during myocardial hyperaemia induced by an intravenous infusion of 0.14 mg×kg^{-1}×min^{-1} dipyridamole (6 min) or adenosine (2 min). An example is given in the online appendix Supplemental Fig. A.1. Care was taken to ensure measurement at the same angle on the same segment of LAD. In case of inadequate quality an intravenous ultrasonic contrast agent (Sulphurhexafluorid [SonoVue, Bracco Imaging Skandinavia AB, Hisings Backa, Sweden] or Perflutren [Optison, GE Healthcare A/S, Brøndby, Denmark]) was applied. CFR was calculated as the ratio between the highest CFV obtained during or after infusion and resting CFV using a mean of three consecutive cardiac cycles. Images were analysed offline by an investigator blinded to all other data. We have previously reported inter and intra-observer variability of repeated off-line CFR readings with within-subject coefficient of variation (CV) of 5.5% ($n = 39$) and 7.5% ($n = 10$), respectively [17]. Resting rate-pressure product (RPP), systolic blood pressure multiplied by heart rate, was obtained as a surrogate for myocardial work.

2.4. Peripheral arterial tonometry (PAT)

Peripheral vascular function was assessed in the morning after an overnight fast by peripheral arterial tonometry (PAT) using plethysmographic finger-cuffs (Endo-PAT2000, Itamar Medical, Caesarea, Israel), which measures arterial pulsatile volume changes. After 5 minutes' baseline measurements, a sphygmomanometric-cuff inflated to ≥200 mm Hg ensured upper arm occlusion of the non-dominant arm for 5 min while the other arm served as a control [16]. The hyperaemic response was recorded after cuff deflation. The reactive hyperaemia index (RHI) was

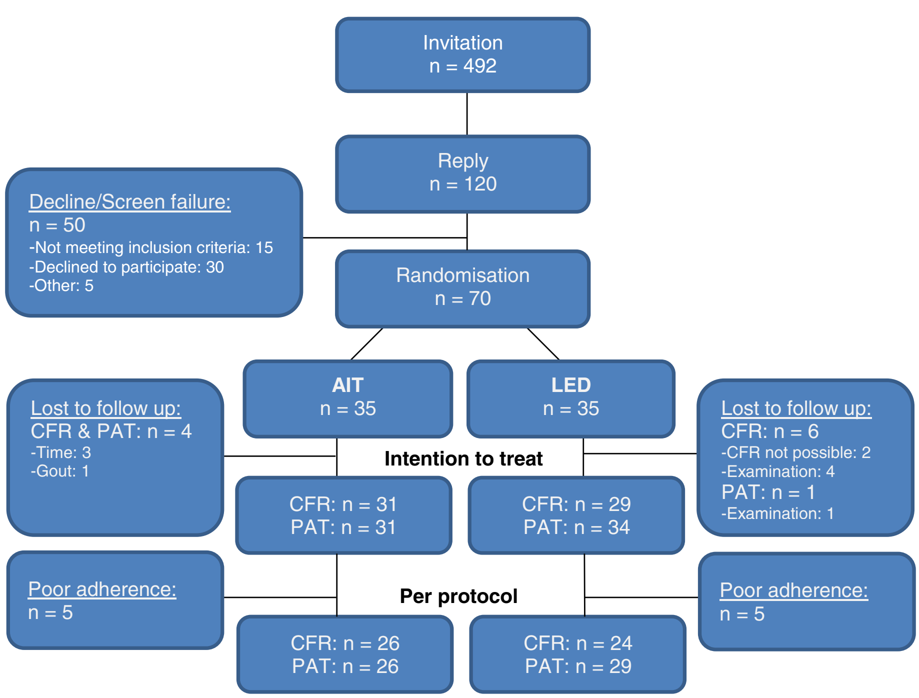

Fig. 1. Inclusion and course of the study. AIT: aerobic interval training. LED: low energy diet. CFR: coronary flow reserve. PAT: peripheral arterial tonometry.