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 ≥60% VO₂peak) 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 VO₂peak and LED in a 10.6% weight loss (between group differences both P < 0.001). CFR increased by 0.26 (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.

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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
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 VO₂peak) or weight loss through 8–10 weeks’ LED (800–1000 kcal·day⁻¹). Cambridge Weight Plan, Northants, UK) followed by a weight maintenance intervention VO₂peak was expressed as mL×(kg FFM)⁻²/₃×min⁻¹. As previously described, body fat mass and fat free mass (FFM) were estimated by whole body dual X-ray absorptiometry, and VO₂peak was measured using a bicycle ergometer and breath-by-breath gas exchange 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 (VO₂peak)

As previously described, body fat mass and fat free mass (FFM) were estimated by whole body dual X-ray absorptiometry, and VO₂peak was measured using a bicycle ergometer and breath-by-breath gas exchange measurements [23]. In order to account for changes in body composition VO₂peak 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 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 Perfluoren [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

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Fig. 1. Inclusion and course of the study. AIT: aerobic interval training. LED: low energy diet. CFR: coronary flow reserve. PAT: peripheral arterial tonometry.
calculated automatically by the Endo-PAT2000 software as the ratio of the occluded arm’s mean pulse wave amplitude (PWA) in the period 90–150 s post deflation to the baseline mean PWA, and then divided by the same ratio of the control arm, and finally multiplied by a baseline correction factor (0.2276 × ln(occluded arm’s baseline mean PWA)-0.2) to account for systemic vascular changes during testing [24]. An alternative reactive hyperaemia score, derived from the Framingham Heart Study, Framingham–RHI (FRHI), was calculated as the natural logarithm of the RHI (based on the interval 90 120 s post deflation) without the baseline correction factor [25].

Augmentation index (AIx) provides a measure of arterial stiffness. As a pulse-pressure wave moves from the left ventricle through the arteries, it encounters higher impedance resulting in a reflected wave that moves backwards. With stiffer arteries the increased pulse wave velocity causes the reflected wave to reach the pulse-wave in the systole rather than the diastole and cause an augmented peak systolic pressure. The Endo-PAT software automatically identified the early systolic pressure (P1) and the pressure corresponding to the reflected peak (P2), and calculated AIx as (P2 − P1) / P1 × 100%. AIx is inversely related to heart rate and was adjusted to a heart rate of 75 beats per minute (AI@75) [26].

2.5. Statistics

The study was designed to detect a true difference between interventions of 10%, equal to a change in CFR of approximately 0.24, with a power of 0.80 and a significance level of 0.05 [22].

Unless stated otherwise, categorical data are presented as number (percentage), continuous data as mean (SD) or median (Q1, Q3) if normal distribution could not be assumed. Differences between groups and changes within and between groups are presented as mean (95%CI) and were compared by x², Fischer’s exact, Student’s-t, Mann–Whitney U or Wilcoxon signed rank test, as appropriate. Linear regression was applied when corrections for base line parameters were made or to evaluate the association between change in CFR and change in other parameters. Analyses were performed in STATA/IC 13.1 (StataCorp LP, College Station, TX, USA).

3. Results

3.1. Population and intervention

Fifty-seven (81%) of the participants were male, median age was 63 (58; 71) years, and median BMI was 31.3 (29.7; 33.7). Participants were generally asymptomatic, well-controlled in terms of blood pressure and lipids, and contemporarily treated with platelet inhibitors, statins, ACE-inhibitors/sangiotensin receptor blockers and beta-blockers. Sixty-five participants were examined at follow-up: 31 in the AIT group and 34 in the LED group (Fig. 1). In the AIT group median training attendance was 81% (range 22%; 94%) and in the LED group median weight loss was 9.7% (range −3.4%; 17.8%). Five participants in each group did not meet the per protocol criteria, leaving 55 participants for the main analyses. Baseline characteristics for participants included in the per protocol analysis are presented in Table 1 (for intention-to-treat analysis see Supplementary Table A.1). Randomization resulted in comparable groups with the exception of a significantly greater proportion with previous myocardial infarction in the LED group.

As previously reported [23], improvement in VO2peak/FFM was 10.4% in the AIT vs −3.0% in the LED group, weight loss was 1.6% vs 10.6% and decrease in fat mass was 5.5% vs 26.6%, respectively (all between-groups P < 0.001).

Intention-to-treat analyses of the study generated similar results and are presented in the online supplemental material.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of participants who completed the trial per protocol.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIT (n = 26)</td>
<td>LED (n = 29)</td>
</tr>
<tr>
<td>Male sex</td>
<td>22 (85%)</td>
</tr>
<tr>
<td>Age [years]</td>
<td>62.3 (5.7)</td>
</tr>
<tr>
<td>BMI [kg·m⁻²]</td>
<td>31.7 (29.6;34.8)</td>
</tr>
<tr>
<td>Body fat [%]</td>
<td>35.0 (6.5)</td>
</tr>
<tr>
<td>VO2peak/FFM [mL·kg⁻¹·min⁻¹]</td>
<td>20.7 (4.9)</td>
</tr>
<tr>
<td>VO2peak/FFM [mL·kg⁻¹·min⁻¹]</td>
<td>124 (25)</td>
</tr>
<tr>
<td>VO2peak/FFM [mL·kg⁻¹·min⁻¹]</td>
<td>54 (47.60)</td>
</tr>
<tr>
<td>Systolic blood pressure [mmHg]</td>
<td>127 (13)</td>
</tr>
<tr>
<td>Diastolic blood pressure [mmHg]</td>
<td>74 (9.1)</td>
</tr>
<tr>
<td>Total cholesterol [mmol·L⁻¹]</td>
<td>4.3 (0.81)</td>
</tr>
<tr>
<td>HDL [mmol·L⁻¹]</td>
<td>40.8 (4.7)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>9 (35%)</td>
</tr>
<tr>
<td>CC-class</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>4 (15%)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
</tr>
<tr>
<td>ACE-inhibitor/ARB</td>
<td>16 (62%)</td>
</tr>
<tr>
<td>Platelet inhibitor</td>
<td>25 (96%)</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>13 (50%)</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>6 (23%)</td>
</tr>
<tr>
<td>Long-acting nitrate</td>
<td>1 (3.9%)</td>
</tr>
<tr>
<td>Cholesterol lowering drug</td>
<td>25 (96%)</td>
</tr>
</tbody>
</table>

Categorical data: number (percentage). Continuous data: mean (SD) or median (Q1, Q3). P value: between-group difference. AIT: aerobic interval training. ARB: angiotensin receptor blocker. LED: low energy diet. LVEF: left ventricular ejection fraction.
without difference between interventions after adjustment for baseline CFR, previous LAD stenosis, or myocardial infarction involving the LAD.

To explore possible dose–response associations between interventions and CFR, linear regressions of percentage change in CFR on percentage change in VO₂peak of the AIT-group and on change of body fat percentage of the LED-group were performed. Change in VO₂peak was associated with improvement in CFR after AIT (β = 0.93, R² = 0.23, P = 0.017), whereas there was no association between change in body fat percentage and improvement in CFR following the LED (P = 0.50). Change in visceral fat volume was assessed by abdominal MRI in a subgroup of the participants [23]. Visceral fat volume was reduced significantly after both interventions with a significantly greater effect in the AIT-group. Percentage change in visceral fat volume was not associated with percentage change in CFR, including when analysing both interventions together and including participants who did not complete the study per protocol (P = 0.82, n = 31).

### 3.3. Peripheral vascular function

Neither baseline RHI, FRHI or age-adjusted AI@75 correlated with VO₂peak (P = 0.93, 0.81 and 0.50) or sex-adjusted fat percentage (P = 0.76, 0.39 and 0.39). Resting PWA, RHI, FRHI AIx and Al@75 were unchanged following both interventions (Table 2). Data for PWA, FRHI and AIx are not shown). For corresponding results of intention-to-treat analysis please see Supplementary Table 2.

### 4. Discussion

This is the first study to evaluate the effect of weight loss on coronary microvascular function in CAD patients and the first to directly compare the effect of exercise training and weight loss on coronary and peripheral vascular function.

The main finding was that exercise training and weight loss were capable of increasing CFR by a comparable magnitude in overweight and obese patients with CAD. Peripheral vascular function assessed by PAT remained unchanged by the interventions.

#### 4.1. CFR

Baseline CFR indicated generally poor coronary microvascular function of this patient group, with the majority having CFR below 2.5, which is regarded as impaired [3,27]. The improvement in CFR following the interventions was caused by augmentation of hyperaemic CFR, whereas resting CFV was unaltered despite a decrease in resting-RPP. This implies that amplified coronary vascular capacity, and not merely reduced resting myocardial oxygen requirement, explains the improved CFR. We interpret this as improved coronary microvascular function.
Coronary microvascular function is a potential limiting factor for exercise capacity in CAD patients [16]. When both exercise and weight loss can improve CFR, synergistic effects could occur if weight loss is followed by exercise training. The “CUT-IT” trial comprises a subsequent 40-week period of AIT for all participants and will evaluate sustainability and the effect of AIT after a considerable weight loss [22].

4.2. Peripheral vascular function

PAT measures did not correlate with VO2peak or measures of body composition at baseline and were unchanged following both interventions. These findings are concordant with previous studies on exercise intervention and PAT in elderly individuals or individuals with already established CAD [35–37], but differ from previous reports of improved FMD of the brachial artery achieved by both weight loss and exercise training [35,38]. It may be questioned whether the lack of effect on RHI truly reflects lack of effect on endothelial function as a large study of exercise-based cardiac rehabilitation showed a significant increase in FMD whereas RHI was unchanged, despite equal between-day reproducibility of the methods [35,39]. RHI is a measure obtained at the fingertips which integrates peripheral vascular function including the microvasculature and as such reflects small artery reactivity. Conversely, FMD evaluates large conduit artery by brachial ultrasound. The majority of studies applying both brachial ultrasound and PAT find no correlation between FMD and RHI, but a significant correlation between RHI and the post-ischemic hyperaemic velocity time integral, i.e., blood volume, which is the base for the increased shear stress that stimulates FMD [40,41]. Whereas NO primarily accounts for dilation in conduit vessels [42], the increase in digital PWA with reactive hyperaemia is a complex response that reflects changes in digital blood flow and microvascular dilation. In addition to local bioactivity of endothelial-derived NO, the digital vasculature is modulated by the autonomous nervous system, and various systemic and paracrine factors [43]. In previous studies, RHI has been inversely associated with cardiovascular risk factors, CAD (both obstructive and non-obstructive) and future events in CAD patients [25,44,45]. These findings make sense if RHI is perceived as a more complex measure of peripheral vascular function. The lack of improvement in RHI following interventions that do improve FMD could reflect that augmentation of peripheral microvascular capacity is more difficult to obtain.

Interestingly, three recent studies in younger populations without established cardiovascular disease report significant improvements in RHI following weight loss obtained by three weeks of LED, 16 or 24 weeks of reduced-energy intake and moderate-intensity exercise, respectively [46–48]. Thus, a potential discrepancy may be related to age or already established cardiovascular disease. However, at least one study reported a significant improvement of RHI following enhanced external counterpulsation in CAD patients [49]. Thus, further appraisal of the hyperaemic PAT response is needed for a clearer view on this topic.

We did not find improvement in arterial stiffness assessed by AIX with either of the two interventions. Our findings concur with the only other study that we know of reporting on weight loss and PAT estimated AIX [46]. However, other measures have indicated reduced arterial stiffness following weight loss in obese individuals without CAD [50,51]. Although CAD and cardiovascular risk factors have been associated with increased AIX derived from PAT [26], our findings are supported by previous exercise intervention studies on PAT derived AIX [36,37]. A recent meta-analysis based on 8 trials comprising 235 individuals also concluded that arterial stiffness is generally unaltered following aerobic training in middle-aged obese populations [52].

4.3. Limitations

All patients were regarded as revascularised before study inclusion and we did not repeat assessment of coronary anatomy immediately before trial start. However, exercise ecg and stress echocardiography were performed at inclusion and these were without limiting angina or signs of ischemia in all patients included in the study. One patient was excluded before randomisation due to signs of ischemia and angioplasty was performed subsequently.

The generalisability of the results is limited by the exclusion of patients with diabetes and more severe systolic heart failure and the results might not be directly transferable to CAD patients with these comorbidities as well as patients with poorly treated hypertension. The same might apply to patients who are just mildly overweight or patients with more extreme obesity.

Most of the participants had previously participated in exercise-based cardiac rehabilitation and were eligible for CUT-IT if they did not participate in exercise sessions more than twice a week. The effects of AIT might therefore be greater in individuals that previously have not
participated in exercise training. This would concur with our finding that the effect of AIT on CFR correlated with the effect on VO2-peak.

5. Conclusions

Twelve weeks’ AIT or LED increased CFR with comparable magnitude, thus both interventions might affect prognosis of CAD through improvement of coronary microvascular function in overweight and obese patients. Whereas the effect of AIT appends to exercise based cardiac rehabilitation as the best documented secondary prevention in CAD, the improvement of coronary microvascular function in overweight and obese patients with exercise training and lifestyle intervention is crucial for primary prevention. This is further shown by the recent report of the Copenhagen study of overweight patients with coronary artery disease undergoing low energy diet or interval training: the randomized CUT-IT trial protocol, Eur. J. Prev. Cardiol. 21 (2014) 39.

The authors report no relationships that could be construed as a conflict of interest.

References


