



openheart Haemostasis and fibrinolysis after regular high-intensity interval training in patients with coronary artery disease: a randomised controlled trial

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Introduction Patients with coronary artery disease (CAD) have prothrombotic changes compared with healthy individuals. Regular exercise reduces cardiovascular mortality in patients with stable CAD. However, the underlying mechanism for the beneficial effect is unknown. We investigated whether regular exercise would inhibit platelet aggregation and thrombin generation and increase fibrinolysis in patients with CAD.

Materials and methods Patients with CAD were randomised 1:1 to a supervised high-intensity exercise training programme or standard care for 12 weeks. Blood samples were obtained at baseline and after 6 and 12 weeks. Platelet aggregation was evaluated with the Multiplate Analyser, thrombin generation using the calibrated automated thrombogram and fibrinolysis employing a clot lysis assay.

Results A total of 169 stable patients with CAD were randomised, and 142 patients (67±9 years, 83% males) completed the study; 64 in the exercise group and 78 in the standard care group. All but one patients received single antiplatelet therapy. From baseline to 12 weeks postintervention (Δ), no significant between-group differences were found in adenosine diphosphate-induced platelet aggregation (Δ -15 aggregation units (AU), AU×min, 95% CI -70 to 40 in the exercise group and Δ -26 AU×min, 95% CI -77 to 26 in the standard care group, $p=0.44$); endogenous thrombin potential (medians: Δ -5%, 95% CI -12 to 3 in the exercise group and Δ -6%, 95% CI -13 to 1 in the standard care group, $p=0.26$); nor in 50% clot lysis time (medians: Δ -9%, 95% CI -23 to 7 in the exercise group and Δ -17%, 95% CI -29 to -3 in the standard care group, $p=0.60$).

Conclusions Twelve weeks of high-intensity whole-body endurance exercise did not affect platelet aggregation, thrombin generation or fibrinolysis in patients with stable CAD.

Trial registration number NCT04268992.

INTRODUCTION

Coronary artery disease (CAD) is one of the leading causes of death worldwide. Guidelines recommend that patients with CAD are offered cardiac rehabilitation with a strong focus on exercise.¹ Regular exercise reduces

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The beneficial effects of exercise training in patients with coronary artery disease may be explained by improved haemostasis and fibrinolysis, however, there is limited knowledge on this topic.

WHAT THIS STUDY ADDS

⇒ High-intensity exercise training for 12 weeks did not affect platelet aggregation, thrombin generation or fibrinolysis in patients with stable coronary artery disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this randomised trial do not support the hypothesis that the health-beneficial effect of regular exercise training are linked to changes in haemostasis or fibrinolysis in patients with stable coronary artery disease.

cardiovascular death and hospital admissions and improves quality of life in patients with CAD,² but the underlying mechanisms have not been defined.

In atherosclerosis, the arterial endothelium is procoagulant and thus adhesive to platelets.³ Endothelial disruption or rupture of an atherosclerotic plaque leads to a haemostatic chain reaction with activated platelets and coagulation, which may result in coronary thrombus formation and acute myocardial infarction.³ Several studies on patients with CAD engaging in regular exercise have shown a significant reduction in platelet aggregation,^{4 5} coagulation⁶ and an increase in fibrinolysis⁷⁻⁹ compared with baseline. In contrast, a recent randomised study showed that one year of exercise training failed to affect markers of procoagulant activity in patients with CAD and type 2 diabetes mellitus.¹⁰

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Only few studies have examined the impact of regular exercise on haemostasis in patients with stable CAD, and the results are diverging. Therefore, the aim of this randomised controlled study was to investigate whether regular supervised high-intensity exercise training affects haemostasis and fibrinolysis in patients with stable CAD. We hypothesised that compared with standard care, regular exercise training would reduce coagulation and platelet aggregation and increase fibrinolysis in patients with CAD.

MATERIAL AND METHODS

Study population

Patients older than 18 years with angiographically confirmed CAD were randomised 1:1 to either standard medical care or high-intensity exercise training in addition to standard care. Throughout the trial, patients in both groups continued their regular medication. Patients allocated to the standard care group were encouraged to maintain their daily routines and not alter their exercise or other lifestyle habits. Patients with a diagnosis of acute coronary syndrome and/or revascularisation within 12 months were excluded. Other exclusion criteria were inability to perform strenuous exercise, anticoagulant treatment, heart failure (ejection fraction <30% or New York Heart Association (NYHA) class >2), implanted implantable cardioverter-defibrillator (ICD) or cardiac resynchronisation therapy (CRT), serious arrhythmia requiring hospitalisation within the past 6 months, severe valvular heart disease, chronic obstructive pulmonary disease GOLD IV and ≤80% participation in exercise sessions during the intervention period (see below). Patients were enrolled at the Department of Medicine, National Hospital of the Faroe Islands, Tórshavn from July 2020 to June 2021. The study was registered at www.clinicaltrials.gov (NCT04268992).¹¹

Exercise test and high-intensity interval training

Peak oxygen uptake ($\text{VO}_{2\text{peak}}$) was measured at baseline and 12 weeks after intervention start on an electronically braked cycle ergometer (Excalibur Sport, Lode, Groningen, Netherlands). All patients randomised to exercise training performed supervised low-volume high-intensity exercise training three times weekly on rowing ergometers (Concept 2 model D w. PM5, Vermont, USA). Each exercise session consisted of 18 active minutes

resulting in a weekly amount of active exercise training of 54 min. The $\text{VO}_{2\text{peak}}$ test protocol and the exercise programme have recently been presented in detail elsewhere.¹¹ The test protocol data demonstrated a 10% increase in $\text{VO}_{2\text{peak}}$ after exercise training, whereas no changes were detected in the standard care group.¹¹

Laboratory methods

Blood samples were obtained at baseline, at 6 weeks and 12 weeks after the start of the intervention (figure 1). Prior to blood sampling, patients were asked to rest for 30 min, avoid food and liquids (except for water) for 1.5 hours and refrain from caffeine-containing drinks for 12 hours and alcohol consumption for 24 hours. Patients took their usual morning medication. Venous blood was drawn by standard venepuncture (21-gauge needle) with a minimum of stasis. The first tube was discarded. Blood samples for haemoglobin, white cell count and platelet parameters were measured in blood samples anticoagulated with EDTA. Creatinine and estimated glomerular filtration rate were determined with a 4.0 mL lithium heparin tube (all tubes from BD Vacutainer, Plymouth, UK). For platelet aggregation, a 1.6 mL tube coated with hirudin (S-Monovette Hirudin, Sarstedt, Nümbrecht, Germany) was used. Blood samples for fibrinogen, international normalised ratio (INR), thrombin generation, clot lysis, plasminogen activator inhibitor-1 (PAI-1), D-dimer and activated partial thromboplastin time (APTT) were drawn using 3.5 mL tubes anticoagulated with 3.2% sodium citrate (Vacuette, Greiner Bio-One, Kremsmünster, Austria). Blood samples were centrifuged for 25 min at 3100 g at 20°C; moreover, the platelet-poor plasma for thrombin generation was centrifuged for further 15 min at 2500 g. All platelet poor plasma was frozen at -80°C until analysed.

Platelets

Samples for platelet aggregation analysis rested between 30 min and 2 hours before assessment with the Multi-plate Analyser (Roche, Basel, Switzerland). Platelet aggregation was initiated with three different agonists: adenosine diphosphate (ADPtest, 6.5 μM), arachidonic acid (ASPItest, 0.5 mM) and thrombin receptor-activating peptide-6 (TRAPtest, 32.3 μM). Aggregation results are presented as area under the curve (aggregation units×min). Platelet turnover was assessed by mean

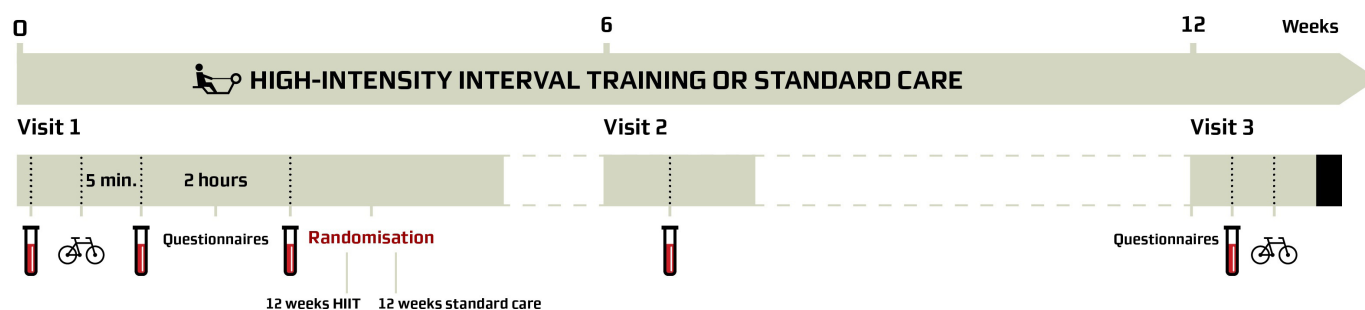


Figure 1 Overview of visits for each patient.

platelet volume (MPV) using Sysmex XN-1000, Norderstedt, Germany.

Coagulation

Thrombin generation was evaluated with the calibrated automated thrombogram (Thrombinoscope BV, Maastricht, the Netherlands). The assay was performed in duplicate on 96-well microtiter plates with 5 pM tissue factor and 4 µM phospholipid. Results were reported as time from start analysis to initiation of thrombin generation (lag-time, min), thrombin amount (area under the curved, labelled endogenous thrombin potential (ETP, nM×min)), maximum thrombin concentration (peak, nM), and time to maximum thrombin concentration (tt-peak, min). Plasma fibrinogen (functional) and INR were measured by ACL TOP 500 CTS (Werfen, Cheshire, UK) and APTT by CS2100i (Sysmex, Norderstedt, Germany).

Fibrinolysis

Clot lysis time was evaluated by an in-house dynamic turbidimetric assay.¹² Briefly, in a 96-well microplate, citrated platelet-poor plasma was mixed with a reaction solution including tissue factor (4 µM phospholipid and tissue factor 1:5000) and tissue plasminogen activator (116 ng/mL, Ca²⁺ 26,7 mmol/L). Plates were read using a Victor X4 (Perkin Elmer, Turku, Finland). The following parameter was recorded: time from peak to 50% lysis of the clot (50% clot lysis time, seconds). D-dimer was measured by CS2100i (Sysmex, Norderstedt, Germany). PAI-1 was analysed in duplicates with an ELISA technique (TECHNOZYM PAI-1 Antigen ELISA Kit, Technoclone).

Randomisation

Randomisation was performed using Microsoft Excel in block sizes of 2, 4, 6 and 8. Letters with 'control' and 'exercise' were wrapped in aluminium paper and sealed in envelopes. The envelopes were numbered according to the randomisation order. The randomisation procedure was performed by an uninvolved person, and the persons performing the project were blinded for the randomisation process.

Statistics

All statistical analyses were performed with SPSS (V.28.0.0.0). P values < 0.05 were considered statistically significant. Our primary outcome was changes in 50% clot lysis time from baseline to 12 weeks after exercise training compared with standard care. Secondary laboratory endpoints were PAI-1, D-dimer, fibrinogen, ETP, platelet turnover, ADP-, ASPI- and TRAP-induced platelet aggregation after 6 and 12 weeks of exercise training compared with standard care. The sample size calculation was based on the primary outcome measure of the between-group difference in 50% clot lysis time after 12 weeks of intervention. Since no data were available on clot lysis time among exercise-trained individuals, we relied on data from our group on healthy individuals for the sample size calculation.¹³ We have previously reported a mean 50% clot lysis time of 521 s with an standard

deviation (SD) of 244 s in drug-naive healthy individuals. Choosing a minimal relevant difference of 25%, a significance level (two-sided alpha) of 5% and a statistical power of 90%, a total of 75 patients had to complete the study in each group. However, 64 and 78 patients completed each group out of a total of 169 included, resulting in an 88% statistical power. Continuous data were evaluated for normality by visual assessment of Q-Q plots and histograms and were reported as means with SD or 95% confidence interval (CI) if normally distributed and as medians (creatinine) with interquartile ranges (IQR) or 95% CI if not. Categorical data were presented as ratios and percentages. For comparison of between-group differences in baseline characteristics, we used an unpaired t-test or Mann-Whitney test for continuous data, and the χ^2 or Fisher's exact test for proportions. For primary and secondary outcomes, comparisons between the two groups were evaluated with a linear mixed model for repeated measures over time by randomisation group (exercise vs standard care) to analyse the impact of exercise training or standard care on several haemostatic variables at baseline and after 6 and 12 weeks with fixed effects of group, time and the interaction of group and time (group×time). The assumptions of homogeneity of variance and normality of residuals were undertaken for all data. Model assumptions for ASPI-induced platelet aggregation, lag time, peak thrombin, ETP, 50% lysis time, PAI-1 and D-dimer were clearly violated, and data were logarithmically transformed to comply to the assumptions. The data were analysed by a sensitivity analysis on all completed cases. We also performed an intention-to-treat analysis on all the outcome parameters, which did not change the results substantially (data not shown).

RESULTS

The flow chart in [figure 2](#) shows that 169 patients with CAD were randomly allocated to high-intensity exercise training (n=83) or standard care (n=86). The drop-out was higher in the exercise group, and the reasons for dropping out are also shown in [figure 2](#). A total of 142 patients completed the study; 64 patients in the intervention group and 78 patients in the standard care group. Baseline characteristics did not differ between the two groups (see [table 1](#)). The mean age of patients was 67 years. The majority of patients were treated with 75 mg acetylsalicylic acid, however, three patients were treated with clopidogrel (in the exercise group) and one patient received no antiplatelet treatment.

Platelets

[Figure 3](#) shows the results of platelet aggregation and MPV, a marker of platelet turnover. After 12 weeks of intervention, there were no within-group or between-group differences in platelet aggregation induced by ADP, ASPI and TRAP (group×time, all p>0.37) or MPV (group×time, p=0.42). Because 97% of the patients are

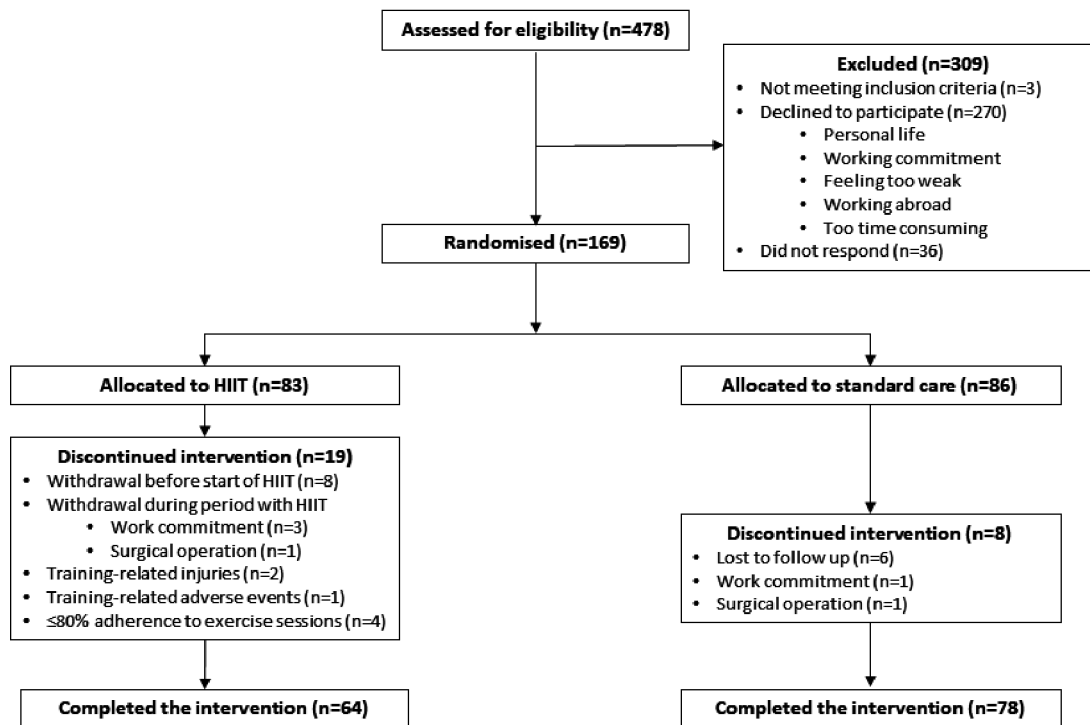


Figure 2 Flow chart of recruitment for the randomised controlled trial. HIIT, high-intensity interval training.

treated with aspirin, the results on ASPI-induced platelet aggregation were much lower than the reference interval (figure 3). All other variables were inside the reference range. Platelet turnover data were available for 73 (51%) patients.

Thrombin generation and standard coagulation

There was a drop in ETP from 1273 nM×min, 95% CI 1198 to 1353 to 1151 nM×min, 95% CI 1082 to 1223 in the exercise group from baseline to 6 weeks following exercise training ($p=0.012$). Furthermore, at 6 weeks after intervention start, ETP in the exercise group was 10%, 95% CI -17 to -2 lower than in the standard care group ($p=0.014$). After 12 weeks of intervention, however, these changes in ETP were no longer significant within or between groups (group×time, $p=0.100$). The remaining three thrombin generation parameters (group×time, all $p>0.23$) and fibrinogen (group×time, $p=0.97$) showed no within-group or between-group variations, as shown in figure 4. All parameters were inside the reference range.¹⁴

Fibrinolysis

We found no differences between groups in clot lysis time, PAI-1 or D-dimer from baseline to after 12 weeks of intervention (group×time, all $p>0.11$, figure 5). However, clot lysis time and PAI-1 were lowered in the standard care group by 20%, 95% CI -32 to -7 and 24%, 95% CI -41 to -3 after 6 weeks ($p=0.002$ and $p=0.024$) and by 18%, 95% CI -30 to -4 and 33%, 95% CI -48 to -14 after 12 weeks of intervention ($p=0.008$ and $p<0.001$). Clot

lysis time and PAI-1 were within the reference interval. D-dimer was above the maximum reference limit of 0.5 (not age corrected).

DISCUSSION

The present randomised controlled study investigated whether 12 weeks of supervised high-intensity interval training affects platelet aggregation, thrombin generation and fibrinolysis in patients with stable CAD. Notably, the applied exercise training intervention did not significantly affect the obtained markers of platelet aggregation, thrombin generation and fibrinolysis.

Platelets play a key role in primary haemostasis. Based on the literature,^{4 5 15 16} we hypothesised that regular exercise training would reduce platelet aggregation and platelet turnover. However, we did not find any changes after 12 weeks of exercise training. Obviously, a potential effect may be blunted by the aspirin treatment, which almost all patients with CAD are treated with. Recently, two studies investigated patients shortly after an acute coronary syndrome under dual antiplatelet therapy. Heber *et al* demonstrated in a randomised controlled trial that high-intensity interval training in combination with moderate-intensity continuous training compared with moderate-intensity continuous training alone resulted in reduced platelet reactivity, but without effect on platelet activation after 12 weeks of exercise.⁴ Tóth-Zsámboki *et al* investigated effects on platelet activation and platelet aggregation after 3 months of conventional cardiac

Table 1 Patient characteristics

Characteristics	All (n=142)	Exercise (n=64)	Standard care (n=78)	P value
Age (years)	66.7±9.4	67.0±9.5	66.4±9.3	0.72
Gender (male/female)	118/24 (83%/17%)	54/10 (84%/16%)	64/14 (82%/18%)	0.71
BMI, kg/m ²	29.4±4.8	29.2±4.9	29.7±4.8	0.52
LVEF (%)	57 (56, 58)	57 (55, 58)	57 (56, 59)	0.65
Revascularisation of CAD and conservative treatment of AMI				
CABG	49 (35%)	24 (38%)	25 (32%)	0.60
PCI	96 (68%)	41 (64%)	55 (71%)	0.47
STEMI or NSTEMI without revascularisation/conservative medical management	8 (6%)	3 (5%)	5 (6%)	0.73
Diagnosis before revascularisation or conservative medical treatment				0.97
Chronic coronary syndrome	47 (33%)	22 (34%)	25 (32%)	
UAP	18 (13%)	8 (13%)	10 (13%)	
NSTEMI	43 (30%)	18 (28%)	25 (32%)	
STEMI	33 (23%)	16 (25%)	17 (22%)	
Ischaemic heart failure	1 (1%)	0 (0%)	1 (1%)	
Predisposing factors and other cardiovascular diseases				
Familial predisposition	35 (25%)	19 (30%)	16 (21%)	0.25
Diabetes	27 (19%)	16 (25%)	11 (14%)	0.13
Hypertension	111 (78%)	50 (78%)	61 (78%)	1.00
Dyslipidaemia treatment	135 (95.1%)	61 (95.3%)	74 (94.9%)	1.00
Smoking				0.38
Never smoked	41 (29%)	22 (34%)	19 (24%)	
Ex-smoker	88 (62%)	36 (56%)	52 (67%)	
Current smoker	13 (9%)	6 (9%)	7 (9%)	
Alcohol consumption				0.14
<7 standard drinks/week	120 (85%)	54 (84%)	66 (85%)	
7–14 standard drinks/week	13 (9%)	4 (6%)	9 (12%)	
>14 standard drinks/week	8 (6%)	6 (9%)	2 (3%)	
Previous apoplexia cerebri	3 (2%)	2 (3%)	1 (1%)	0.59
Claudicatio intermittens	3 (2%)	2 (3%)	1 (1%)	0.59
Charlson Comorbidity Index	3.8±1.5	4.0±1.8	3.7±1.3	0.27
Biochemistry				
Creatinine (µmol/L)	81±21	79±22	82±21	0.44
eGFR (mL/min/1.73 m ²)	79±14	79±15	79±13	0.86
Total cholesterol (mmol/L)	3.6±0.7	3.5±0.6	3.6±0.7	0.24
LDL-C (mmol/L)	1.7±0.5	1.7±0.5	1.8±0.5	0.32
HDL-C (mmol/L)	1.2±0.3	1.2±0.3	1.2±0.4	0.72
Triglycerides (mmol/L)	1.5±1.1	1.4±0.7	1.6±1.3	0.49
HbA1c (mmol/mol)	41±10	43±12	40±8	0.17
Platelet count (×10 ⁹ /L)	210±54	204±48	214±58	0.28
APTT (sec), median	26 (1)	26 (1)	26 (1)	0.95
INR	1.0±0.1	1.0±0.1	1.0±0.1	0.77
Medication				
Aspirin	138 (97%)	60 (94%)	78 (100%)	0.04

Continued

Table 1 Continued

Characteristics	All (n=142)	Exercise (n=64)	Standard care (n=78)	P value
Clopidogrel	3 (2%)	3 (5%)	0 (0%)	0.09
Beta blocker	92 (65%)	45 (70%)	47 (60%)	0.22
ACE inhibitor	54 (38%)	31 (48%)	23 (30%)	0.02
Angiotensin II receptor blockers	35 (25%)	12 (19%)	23 (30%)	0.17
Statins	131 (92%)	60 (94%)	71 (91%)	0.75
Ezetimibe	30 (21%)	16 (25%)	14 (18%)	0.41
Calcium antagonists	54 (38%)	21 (33%)	33 (42%)	0.30
Nitrates	18 (13%)	8 (13%)	10 (13%)	1.00
Diuretics	31 (22%)	12 (19%)	19 (24%)	0.54

Continuous variables are presented as means±SD or as medians with IQR; dichotomous variables are expressed as numbers and percentages.

ACE, Angiotensin-converting enzyme; AMI, acute myocardial infarction; APTT, activated partial thromboplastin time; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HbA1c, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HIIT, high-intensity interval training; INR, international normalised ratio; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; UAP, unstable angina pectoris.

rehabilitation or a new complex cardiac rehabilitation programme in a non-randomised controlled trial. They reported significantly reduced platelet aggregation after the complex cardiac rehabilitation, however, these findings may partly be explained by the management of several cardiovascular risk factors. As in our study,

Tóth-Zsámboki *et al* reported no changes in MPV.⁵ In contrast, Durmuş *et al* reported that patients with CAD who underwent cardiac rehabilitation displayed a lower MPV than those who did not.¹⁷ Moreover, Keating *et al* performed a randomised controlled study on the effect of 4-month combined exercise and behavioural weight

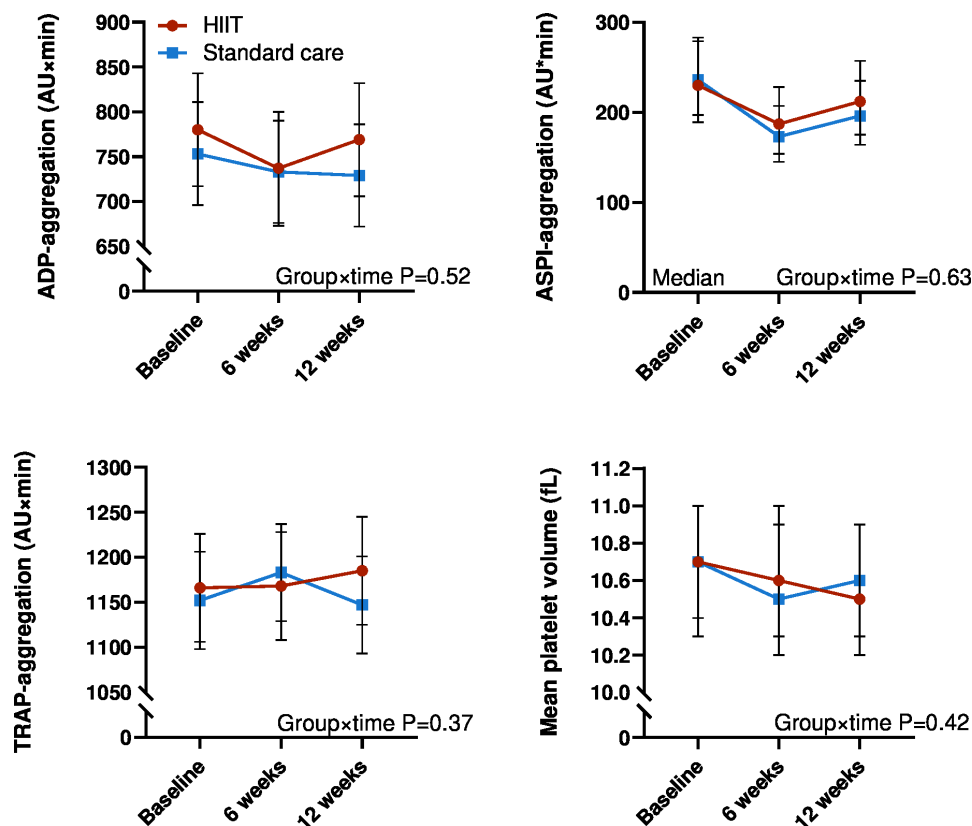


Figure 3 Platelet aggregation and mean platelet volume. Values are presented as means or medians with 95% CI. P values represent a linear mixed-model testing with group, time and group×time interaction as fixed factors. AU, aggregation unit; HIIT, high-intensity interval training; TRAP, thrombin receptor activating peptide-6.

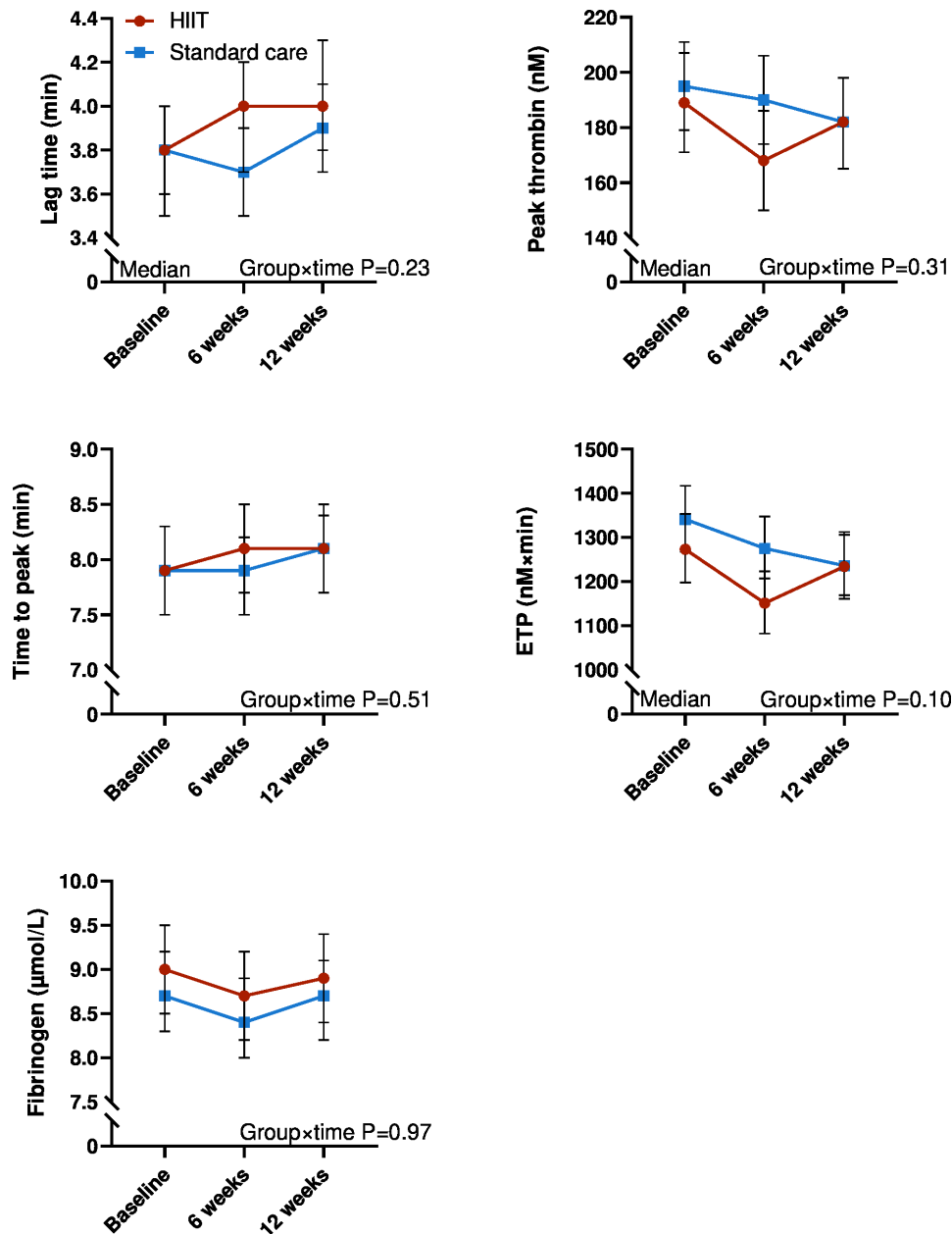


Figure 4 Thrombin generation parameters and fibrinogen. Values are presented as means or medians with 95% CI. P values represent a linear mixed-model testing with group, time and group×time interaction as fixed factors. ETP, endogenous thrombin potential; HIIT, high-intensity interval training.

loss on platelet reactivity in 46 patients with CAD. They found that exercise and weight loss were associated with decrease in platelets expressing P-selectin but not in GPIIb-IIIa activation.¹⁶ Lee *et al* randomised patients with CAD to hospital-based cardiac rehabilitation or home-based cardiac rehabilitation, which decreased von Willibrand factor but not soluble P-selectin in both groups, with no differences between the two programmes.¹⁵ These results are in contrast to our study, which showed no differences when comparing high-intensity exercise training with standard care. The biggest difference between our and the previous studies is that the other studies enrolled patients shortly after an acute coronary event. It has previously been shown that platelets are more

active up to at least 6 months after ST-segment myocardial infarction compared with patients with stable CAD,¹⁸ and this may explain the different results.

From baseline to after 12 weeks' intervention, we found no differences in thrombin generation or fibrinogen between the patients who performed exercise training or continued standard care. At 6 weeks, however, the thrombin generation parameter, ETP, was reduced in the exercise group compared with baseline and with standard care. This reduction was no longer present after 12 weeks. However, ETP tended to be lower in both groups after 12 weeks, although most profoundly after 6 weeks in patients who had exercised. This may be explained by random variation in ETP or it could be induced by the

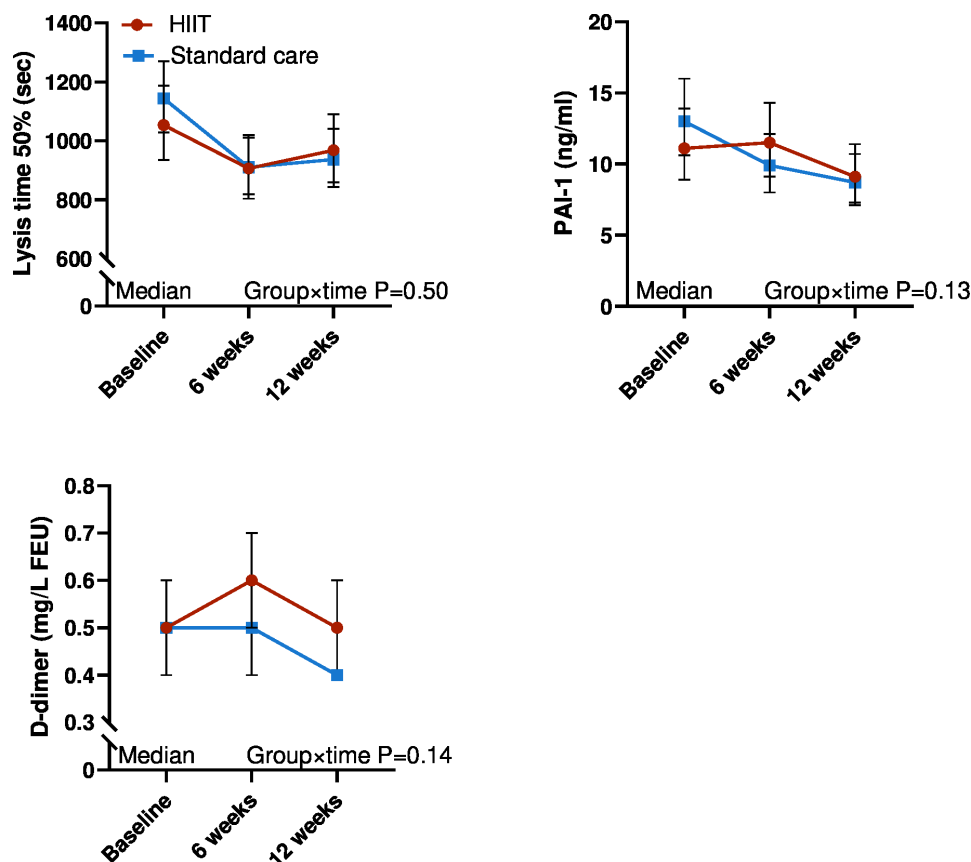


Figure 5 Fibrinolysis investigated by 50% clot lysis time, plasminogen activator inhibitor-1 and D-dimer. Values are presented as medians with 95% CI. P values represent a linear mixed-model testing with group, time and group×time interaction as fixed factors. FEU, fibrinogen equivalent units; HIIT, high-intensity interval training; PAI-1: Plasminogen activator inhibitor-1.

intervention. The exercise programme contained similar intervals throughout the whole training period, however, the first 2 weeks were with lower intensity focusing on familiarisation to the rowing ergometer and rowing technique. In comparison, another study observed a reduction in fibrinogen midway during an intervention of high-intensity interval training in healthy young men where it returned to baseline values after 8 weeks of training.¹⁹ Theoretically, high-intensity interval training may have a favourable effect on coagulation for shorter periods that may reverse if continued over a longer period. In accordance with our findings, a randomised controlled trial by Bratseth *et al*,¹⁰ which included patients with both CAD and diabetes mellitus, found no between-group effect of 12 months exercise training compared with standard care on thrombin generation, free and total tissue factor pathway inhibitor and prothrombin fragment 1+2. In contrast to our results, they reported increased thrombin generation (increased peak and velocity index and decrease in tpeak) in both groups after 12 months of intervention. Previously, three studies have reported a reduction in fibrinogen after exercise training in patients with CAD.^{6 7 20} Suzuki *et al* performed a non-randomised study including patients 1 month after acute coronary syndrome. One month of moderate-intensity continuous training lowered fibrinogen, coagulation factor VIII and von Willebrand factor antigen in the exercise group

only.⁶ Wosornu *et al* investigated patients with CAD within 1 year after coronary artery bypass graft surgery. A total of 55 men were randomised to no formal exercise training, 6 months of aerobic high-intensity exercise training or 6 months of power exercise training. Aerobic exercise training reduced fibrinogen levels after both three and 6 months, while no changes were observed in the power exercise group.⁷ In addition, a community-based study by Nagy *et al* reported reduced von Willebrand factor antigen, coagulation factor VII antigen and fibrinogen in physically active women who survived an acute coronary syndrome.²⁰ In summary, these three studies reported a decrease in several standard coagulation parameters in physically active patients with CAD compared with inactive patients. Importantly, most of the above-mentioned studies have apparent weaknesses concerning their non-randomised design, low sample size, inclusion shortly after an acute coronary event or low adherence to exercise training. Thus, including our study, two randomised controlled studies report no between-group differences on thrombin generation, fibrinogen, free and total tissue factor pathway inhibitor and prothrombin fragment 1+2 after either high-intensity interval training for 12 weeks or a combination of high-intensity exercise training and moderate-intensity continuous training for 12 months.¹⁰

We used a clot lysis assay, PAI-1 and D-dimer to assess fibrinolysis. We found no between-group differences

from baseline to after 12 weeks' intervention. However, at 6 and 12 weeks, there was an unexplained change in fibrinolysis in the standard care group, with a decrease in clot lysis time and PAI-1. These two findings imply an enhanced fibrinolysis over the course of 12 weeks in the standard care group. In the exercise group, clot lysis time also declined after 6 weeks. Despite the short period, these results are in contrast with the fact that fibrinolytic activity decreases with age and that exercise training is suggested to increase fibrinolysis.^{21 22} The mechanisms for these findings are unclear. It may be speculated that patients in the standard care group might have increased their physical activity throughout the intervention period, although the group's stagnant VO_{2peak} testifies against this.¹¹ Several other studies have investigated the effect of exercise training on fibrinolysis, but the results are conflicting. Two non-randomised studies reported a reduction in PAI-1 and thereby an increased fibrinolysis after 8 weeks or 9 months of exercise.^{9 23} In contrast, three non-randomised studies found no changes in PAI-1^{20 24} or tissue plasminogen activator^{9 24} after regular exercise training. Two randomised controlled investigations reported no effect of regular exercise training on D-dimer in patients with CAD,^{10 25} whereas one study found that it decreased following cardiac rehabilitation.¹⁵ An important difference between the current study and most of the previous ones is that patients with CAD underwent regular high-intensity exercise training as opposed to moderate-intensity continuous training. The two training modes likely stimulate different physiological pathways.^{26 27} Numerous studies have shown that high-intensity interval training is superior to moderate-intensity continuous training in terms of increasing peak oxygen uptake in patients with CAD^{28 29}; but the impact on other parameters has not been thoroughly examined. However, in postinfarction heart failure patients Wisløff *et al*³⁰ demonstrated that high-intensity interval training was more effective than moderate-intensity continuous training at reversing left ventricular remodelling, endothelial function and mitochondrial function.

Strengths and limitations

The patients with CAD included in our study were at least 12 months beyond an acute myocardial infarction or coronary intervention, whereas most previous studies on regular exercise effects on haemostasis were performed in patients recently diagnosed with acute myocardial infarction. Thus platelet function¹⁸ and haemostasis³¹ may not have reached a steady state. The randomised controlled design and the sample size of this study are also major strengths, allowing us to draw more firm conclusions. A randomised design is preferable because any unmeasured confounders are equally distributed between groups. Moreover, adherence to the exercise protocol was very high (97%) and the efficiency of the applied exercise training programme was confirmed by the ~10% improvement in peak oxygen consumption in the exercise group only.

Single antiplatelet therapy with aspirin challenges the ability to measure effects of exercise training on platelet aggregation, however, it would be unethical to discontinue these therapies. Other widely used medications may also influence or omit potential findings in this patient group, for example, ACE inhibitors, angiotensin-receptor II blockers and statins.

Conclusion

Regular whole-body high-intensity exercise training did not affect platelet aggregation, thrombin generation or fibrinolysis in patients with CAD. Thus, our findings indicate that the well-documented health benefits of exercise training in CAD are most likely not explained by changes in platelet aggregation, thrombin generation or fibrinolysis.

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