**Predictors of response to exercise training in patients with coronary artery disease – a subanalysis of the SAINTEX-CAD study**

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**Abstract**

Exercise training (ET) improves peak oxygen uptake ($VO_2$peak), an important predictor of mortality in coronary artery disease (CAD) patients. The influence of clinical and disease characteristics on training response is not well established in CAD. Therefore, we aimed to evaluate whether baseline cardiovascular disease variables and training intensity can predict the maximal aerobic response to ET. The Study on Aerobic INTerval EXercise training in CAD patients (SAINTEX-CAD) previously showed that 12 weeks of aerobic interval training and continuous training equally improved $VO_2$peak in CAD patients. We identified 24 exercise non-responders (ENR, change $VO_2$peak <1 ml/kg/min) among 167 participants to SAINTEX-CAD. In a between-group comparison, ENR were older, their baseline $VO_2$peak and oxygen uptake efficiency slope (OUES) were higher, and ENR were more frequently included after elective percutaneous coronary intervention (PCI) (all $p<0.05$). In a logistic regression analysis, age (odds ratio (OR)=1.11 (1.04-1.18), p=0.001), history of elective PCI (OR=3.31 (1.12-9.76), p=0.030) and higher baseline $VO_2$peak (OR=1.16 (1.06-1.27), p=0.001) were independent predictors of exercise non-response. In a linear regression analysis, age (ß=-0.605, p=0.001), history of elective PCI (ß=-15.401, p=0.010), training intensity (ß=0.447, p=0.008), baseline physical activity (ß=0.014, p=0.003) and OUES (ß=-0.014, $p<0.001$) independently predicted change in $VO_2$peak and explained 41% of the variability in change in $VO_2$peak.

To summarize, 14% of CAD patients were ENR. Higher baseline $VO_2$peak and OUES, history of elective PCI, older age, lower training intensity and lower baseline physical activity were independent predictors of training non-response. Identification of patients with a large likelihood of non-response is a first step towards patient tailored exercise programmes.

**Abstract word count:** 256



**Keywords**

Coronary artery disease, exercise training, $VO_2$peak response

## Background

Cardiac rehabilitation, including exercise training (ET), improves quality of life, morbidity and mortality in coronary artery disease (CAD) and has gained a class 1, level of evidence A recommendation (1). A 1 ml/kg/min higher peak oxygen uptake ($VO_2$peak) has been associated with a 15% decrease in all-cause and cardiovascular mortality in CAD (2). Unfortunately, 21-23% of patients fail to show a favourable $VO_2$peak response to training (3-5). Apart from genetics, sex, age and comorbidities, baseline physical fitness, physical activity and exercise dose are at play in the general population, but this has not been studied extensively in CAD (6).

## Aims

We assessed whether cardiovascular risk factors, cardiopulmonary exercise test (CPET) variables, training intensity and physical activity can predict the $VO_2$peak response to exercise training in CAD patients. Early identification of $VO_2$peak non-responders could assist in personalisation and optimisation of exercise prescription.

## Methods

We performed a subanalysis of the Study on Aerobic INTerval EXercise training in CAD patients (SAINTEX-CAD). In SAINTEX-CAD, patients with normal left ventricular ejection fraction and either stable CAD (after elective percutaneous coronary intervention (PCI), conservative treatment, or coronary artery bypass graft (CABG)) or acute coronary syndrome (after primary PCI or CABG) were randomised to 12 weeks of aerobic interval training (AIT) or aerobic continuous training (ACT) (7). We studied 167 of 200 patients, in whom $VO_2$peak after 12 weeks was available. Non-response was defined as a change in $VO_2$peak ($\Delta VO_2$peak) of <1 ml/kg/min (2). Maximal CPET was performed on a bicycle ergometer (Ergoline Schiller). Training intensity was defined as percentage of average heart rate over all sessions divided by baseline peak heart rate. Training adherence was recorded as number of training sessions completed. Physical activity during the first training week was evaluated in 75 patients using SenseWear Pro3 ArmbandTM (BodyMedia) (8).

Statistical analyses were performed using SPSS v24.0 (IBM). Baseline characteristics were analysed with independent samples T-test (normally distributed variables), Mann-Whitney U test (skewed variables) and chi-square test (categorical variables). Pearson (normally distributed variables) and Spearman (skewed variables) correlation coefficients were calculated between baseline variables and $\Delta VO_2$peak. Multiple linear regression models ($\Delta VO_2$peak, method 'backward', variables in 1 block: sex, age, elective PCI, oxygen uptake efficiency slope (OUES), training intensity, steps/12h, energy expenditure/12h and sedentary time/12h) and multiple logistic regression models (responder status, method 'enter', variables in 1 block: age, elective PCI and baseline $VO_2$peak) were used to assess independent determinants of training response.

## Results

Of 167 included patients (155 males), 24 were $VO_2$peak non-responders (14%, 22 males, 46% AIT).

Baseline characteristics according to responder status are shown in Table 1. Pharmacological therapy was similar between groups (all $p > 0.05$, data not shown). Non-responders were older patients ($p=0.009$), more frequently included after elective PCI ($p=0.007$) and had a lower prevalence of diabetes mellitus ($p=0.029$). Non-responders had higher baseline $VO_2$peak, OUES, % predicted $VO_2$peak and % predicted workload compared to responders (all $p<0.05$). Actual training intensity and training adherence were similar between responders and non-responders. Non-responders showed a trend towards higher sedentary time, less energy expenditure and fewer steps (/12h, all $p>0.05$).

In a multivariate analysis (Table 2), age, baseline $VO_2$peak, %predicted $VO_2$peak, %predicted workload and OUES were negatively correlated with $\Delta VO_2$peak, whereas training intensity was positively correlated with $\Delta VO_2$peak. Again, $\Delta VO_2$peak was related to baseline physical activity, with lower energy expenditure and steps/12h, and higher sedentary time/12h resulting in a lower $\Delta VO_2$peak.

In a linear regression analysis, older age, history of elective PCI, higher OUES, lower training intensity and lower baseline energy expenditure were independent predictors of a lower $\Delta VO_2$peak (Table 2). This model explained 41% of the variability in $\Delta VO_2$peak. In logistic regression analyses older age, history of elective PCI and higher baseline $VO_2$peak were independent predictors of non-response to exercise training (Table 2).

**Conclusion**

In this subanalysis of SAINTEX-CAD, 24 out of 167 CAD patients (14%) were $VO_2$peak non-responders, equally distributed across both training regimes. Older age, inclusion after elective PCI, higher baseline $VO_2$peak and OUES, lower training intensity and lower baseline energy expenditure were predictors of impaired $VO_2$peak trainability. Older age, inclusion after elective PCI, higher baseline OUES and lower training intensity and baseline energy expenditure explained 41% of the variability in $\Delta VO_2$peak. By carefully assessing these variables upon inclusion for cardiac rehabilitation, ENR can be identified early and this could be a first step towards patient tailored exercise prescription.

Older age, higher baseline exercise performance, lower training frequency and intensity have been described as predictors of training non-response (4,9). Patients who underwent PCI had a lower improvement in $VO_2$peak compared to CABG or AMI, which was partly explained by the higher baseline exercise performance in these patients (9). In the present study, non-responders were possibly more physically active prior to engaging in CR. However, this could not be confirmed by physical activity state prior to rehabilitation. Possibly, non-responders had a higher baseline $VO_2$peak due to better physical fitness, despite their sedentary state.

Patients that already had a high OUES at baseline, showed less improvement in $VO_2$peak following 3 months of exercise training. OUES is strongly related to $VO_2$peak (10) and is an independent predictor of all-cause and cardiovascular mortality in CAD patients (11). Furthermore, a high $VO_2$peak at baseline also resulted in a lower increase in $VO_2$peak, which is consistent with previous studies (5,12,13). Whether increasing training duration, intensity or frequency can improve the $VO_2$peak response in these patients remains to be determined in larger trials.

Table 1: Univariate analysis: difference between non-responders and responders

| | Baseline parameters | Non-responders n=24 | Responders n=143 | p |
|---|---|---|---|---|
| **CV risk factors** | Age (years) | 63.1 (±8.1) | 58.0 (±8.9) | **0.009** |
| | Sex | 22 men (92%) | 133 men (93%) | 0.684 |
| | BMI ($kg/m^2$) | 26.7 (22.3-39.9) | 28.0 (19.8-36.7) | 0.418 |
| | History of hypertension | 11 (46%) | 77 (54%) | 0.467 |
| | History of diabetes mellitus | 1 (4%) | 34 (24%) | **0.029** |
| | Total cholesterol | 152.9 (±27.6) | 135.7 (±27.4) | **0.005** |
| | LDL cholesterol | 83.4 (±23.6) | 71.8 (±21.2) | **0.015** |
| | HDL cholesterol | 49 (27-67) | 42 (18-85) | 0.073 |
| | Triglycerides | 104 (53-562) | 105 (51-567) | 0.769 |
| **Type of CAD** | Stable CAD post-CABG | 3 (13%) | 44 (31%) | 0.066 |
| | Stable CAD elective PCI | 8 (33%) | 15 (10%) | **0.007** |
| | ACS conservative | 0 | 7 (5%) | 0.595 |
| | ACS CABG | 0 | 3 (2%) | 1.0 |
| | ACS primary PCI | 13 (54%) | 74 (52%) | 0.826 |
| **CPET** | Resting HR (bpm) | 61 (49-76) | 65 (37-100) | 0.090 |
| | $VO_2$peak (l/min) | 2.05 (1.1-3.5) | 1.89 (0.9-3.4) | **0.044** |
| | $VO_2$peak (ml/kg/min) | 25.2 (16.8-46.2) | 22.1 (9.8-33.5) | **0.042** |
| | % predicted $VO_2$peak (%) | 102.8 (±26.9) | 81.3 (±19.4) | **0.001** |
| | Work economy (watt/ml/kg/min) | 0.30 (0.21-0.51) | 0.28 (0.14-0.45) | 0.083 |
| | Resting systolic BP (mmHg) | 123 (±18.5) | 119 (±16.5) | 0.339 |
| | Peak systolic BP (mmHg) | 182 (±30.5) | 172 (±28.6) | 0.111 |
| | Peak work load (Watt) | 160 (60-240) | 140 (60-260) | 0.246 |
| | % predicted work load (%) | 124.4 (59.4-180.3) | 96.4 (32.0-179.5) | **0.007** |
| | OUES | 2106.1 (849.7-3910.4) | 1873.8 (920.1-3615.3) | **0.020** |
| | VE/VCO2 slope | 31.1 (20.3-47.3) | 29.9 (17.0-49.6) | 0.475 |
| **Training** | Group assignment AIT/ACT (n, %) | AIT 11 (46%)<br>ACT 13 (54%) | AIT 71 (50%)<br>ACT 72 (50%) | 0.729 |
| | Training intensity (%) | 79.9 (±9.5) | 84.8 (±9.6) | 0.104 |
| | Adherence (number of training sessions) | 36 (32-36) | 36 (30-42) | 0.224 |
| **Physical activity** | | **n=12** | **n=63** | |
| | On-body time (h) | 69.5 (64.8-81.9) | 70.4 (34.6-117.5) | 0.902 |
| | Sedentary time per 12h | 10.7 (9.0-11.4) | 10.2 (6.4-11.7) | 0.059 |
| | Total energy expenditure (on-body, per 12h) | 1528.7 (1118.1-2213.1) | 1688.0 (1245.0-3552.4) | 0.071 |
| | Total number of steps per 12h | 4898.6 (±1669.3) | 6081.9 (±2213.7) | 0.083 |

ACS= acute coronary syndrome, ACT= aerobic continuous training, AIT= aerobic interval training, BMI= body mass index, BP= blood pressure, CABG= coronary artery bypass graft, CAD= coronary artery disease, CPET= cardiopulmonary exercise test, CV= cardiovascular, HR= heart rate, OUES= oxygen uptake efficiency slope, PCI= percutaneous coronary intervention.

Table 2: Multivariate analysis: Association of change in $VO_2$peak with baseline variables

| | Baseline parameters | Correlation | | Linear regression | | Logistic regression | |
|---|---|---|---|---|---|---|---|
| | | r | p | ß (95% CI) | p | Odds ratio (95% CI) | p |
| **CV risk factors** | Age (years)* | -0.238 | 0.002 | -0.605 (-0.94 – -0.27) | 0.001 | 1.11 (1.04 – 1.18) | 0.001 |
| **Type of CAD** | Elective PCI | - | - | -15.401 (-26.96 – -3.84) | 0.010 | 3.31 (1.12 – 9.76) | 0.030 |
| **CPET** | $VO_2$peak (mL/kg/min)* | -0.238 | 0.002 | - | - | 1.16 (1.06 – 1.27) | 0.001 |
| | % Predicted $VO_2$peak (mL/kg/min)* | -0.380 | <0.001 | - | - | - | - |
| | %Predicted workload (W)* | -0.292 | <0.001 | - | - | - | - |
| | OUES** | -0.182 | 0.019 | -0.014 (-0.02 – -0.01) | <0.001 | - | - |
| **Training** | Training intensity (%)* | 0.315 | 0.004 | 0.447 (0.12 – 0.77) | 0.008 | - | - |
| **Physical activity** | Baseline energy expenditure/12h (kcal/12h)* | 0.261 | 0.024 | 0.014 (0.01 – 0.02) | 0.003 | - | - |
| | Steps/12h* | 0.329 | 0.004 | - | - | - | - |
| | Sedentary time/12h** | -0.235 | 0.043 | - | - | - | - |

*Pearson or **Spearman correlation. CAD = coronary artery disease, CI = confidence interval, CPET = cardiopulmonary exercise test, CV = cardiovascular, OUES= oxygen uptake efficiency slope, PCI = percutaneous coronary intervention, $VO_2$peak = peak oxygen uptake.

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