Influence of Dynamic Training on Hemodynamic, Neurohormonal Responses to Static Exercise and on Inflammatory Markers in Patients After Coronary Artery Bypass Grafting

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Background: Little is known about the influence of dynamic training on the hemodynamic and neurohormonal responses to static exercise and on inflammatory markers in optimally treated post-coronary artery bypass grafting (CABG) patients.

Methods and Results: One hundred and twenty male patients, aged 55±6 years, 3 months after receiving CABG, were randomized to either 6 weeks of aerobic training on a cycloergometer, 3 times a week, at a 70–80% of the maximum tolerated heart rate (HR) (training group, n=60) or to a control group (n=60). At baseline and at the end of the study, all patients underwent: (1) a cardiopulmonary test; (2) handgrip at 30% of maximal voluntary contraction for 3 min in a sitting position during in which HR, blood pressure (BP), stroke volume (SV, by impedance cardiography), cardiac output (CO) and total peripheral resistance (TPR) were monitored; and (3) plasma level assessment of catecholamines, nitric oxide and inflammatory markers. During the final tests, handgrip-induced increases in HR, BP, and TPR (14% vs 27%, P<0.01) were lower, whereas SV and CO were higher (by 13% and 15%, respectively, P<0.05) in trained patients compared with controls. Moreover, a higher increase in nitric oxide level (46% vs 14%, P<0.01) and a lower increase in noradrenaline (11% vs 20%, P<0.05) were observed in trained patients compared with controls. Accordingly, training caused significant improvement in peak oxygen uptake per kilogram body weight (peak VO₂) and inflammatory markers.

Conclusions: Short-term dynamic training caused significant improvement of hemodynamic and neurohormonal responses to handgrip, cardiovascular fitness and inflammatory state. (Circ J 2010; 74: 2598–2604)

Key Words: Coronary artery bypass grafting; Dynamic training; Handgrip; Inflammatory markers

Static efforts are very common in everyday life and are known to activate the sympathetic nervous system abruptly. It is well known that dynamic training positively influences hemodynamic responses to exercise. However, there are no data available on the effect of dynamic training on hemodynamic responses to such stimuli as static exercise (handgrip) in patients with coronary artery disease (CAD) and after coronary artery bypass grafting (CABG).

Little is known about the role of neurohormones during static exercise. The influence of noradrenaline, adrenaline and endothelin-1 during handgrip was studied in healthy subjects or in heart failure patients only, and the role of nitric oxide (NO) in this setting in humans has not been studied at all.1–4 Furthermore, the significance of inflammatory markers in CAD patients is widely recognized; yet, this issue has not been studied in optimally treated post-CABG trained vs...
untrained patients. Therefore, we sought to determine the influence of short-term dynamic training on the hemodynamic and neurohormonal responses to static exercise (handgrip) and on inflammatory markers in optimally treated post-CABG patients.

Methods

From June 2005 to July 2008, 372 consecutive male patients, 3–4 months after CABG, were referred to the Department of Cardiac Rehabilitation, Institute of Cardiology, were screened for inclusion to the study.

The inclusion criteria included: age <65 years, CABG without cardio-pulmonary bypass ≥3 months before recruitment, preserved left ventricular function (ejection fraction >50%), and no evidence of right ventricular dysfunction on echocardiography. The exclusion criteria included: recent myocardial infarction or unstable angina (<3 months), silent ischemia and/or positive exercise stress test at entry, viral and/or bacterial infections during the postoperative period, congestive heart failure, uncontrolled hypertension (blood pressure (BP) >160/100 mmHg at rest), cardiac rhythm disturbances, valvular heart disease, diabetes mellitus, hypercholesterolemia (total cholesterol >5.2 mmol/L), current smoking, chronic obstructive pulmonary disease, peripheral vascular disease, impaired renal or hepatic function, hematological disorders, any form of neoplastic disease, acute infection, chronic inflammatory disease, chronic treatment with corticosteroids, non-steroidal anti-inflammatory drugs or oral anticoagulants, and a lack of patient’s consent. After exclusions, 120 patients were enrolled into the study protocol.

All patients were in sinus rhythm and agreed not to change their low-fat diet, and to maintain a stable level of physical activity during the study. Medications were not altered within 4 weeks prior to enrollment and throughout the duration of the study.

The Institutional Ethics Committee approved the study protocol, and an informed written consent was obtained from each patient.

Study Design

At entry, eligible patients underwent a clinical examination, a symptom-limited cardiopulmonary exercise test with gas exchange measurements (cardiopulmonary exercise test (CPET)), a 2-dimensional echocardiography, a handgrip test, and laboratory analyses, which included a complete blood count, plasma determination of biochemical parameters (e.g., glucose, lipid profile, creatinine, liver function) and inflammatory markers such as fibrinogen, C-reactive protein (CRP), and interleukin-6 (IL-6).

After undergoing baseline measurements, patients were randomized either to a 6-week supervised training program (training group) or to an age-matched control group.

The following examinations were repeated after 6 weeks: a handgrip test with hemodynamic monitoring and plasma neurohormonal assessment, before and at the end of each handgrip, including: catecholamines (adrenaline, noradrenaline), endothelin-1 and NO; and (3) CPET.

Training Program

The training program consisted of 18 interval trainings on a cycloergometer 3 times a week for 6 weeks. Each session was performed for 60 min under continuous electrocardiographic monitoring with the target of 70–80% of maximal heart rate (HR) achieved during CPET. The exercise loads were applied in an interval manner, that is, 4-min exercise bouts with 2-min rests in between. HR and BP were measured at baseline, at the end of each interval and at recovery.

Control patients were instructed to maintain their habitual activities.

Laboratory Measurements

Blood samples for complete blood count, biochemical tests and inflammatory markers were taken between 08:00 and 09:00 h after an overnight fast and routine measurements (eg, blood glucose, lipid profile) were performed immediately using standard laboratory techniques.

To measure plasma levels of catecholamines (adrenaline, noradrenaline), endothelin-1, NO and IL-6, blood was drawn into vacutainers containing EDTA. Plasma was immediately separated by centrifugation at 2,000 g for 10 min at 4°C and the samples were frozen and stored at –70°C until analysis.

High sensitive CRP (hsCRP) and fibrinogen were measured as indices of systemic inflammation by turbidimetric immunoassay and STA Fib2 test (Roche Diagnostics Vienna, Austria) according to the respective manufacturer’s recommendations.

Plasma concentrations of noradrenaline and adrenaline were determined by radioimmunoassay using tests produced by BioSource Europe S.A., Belgium (2 CAT RIA).

Concentrations of endothelin-1 and IL-6 were measured by using an ELISA system with microplate R&D using commercial kits: BI-20052 Endothelin, Biomedica and human IL-6 BMS213 INSTCE, Bender MedSystems, Austria.

The plasma NO level was determined using a blood sample and was quantitatively measured as total nitrate plus nitrite concentrations using a commercially available Nitric Oxide Colorimetric Assay Kit produced by Medical and Biological Laboratories (Woburn, MA, USA). The detection limit of the assay was 0.1 nmol/l nitrite in the sample.

CPET

All patients underwent symptom-limited CPET according to a modified Bruce protocol, using a Schiller treadmill (Carrollton, USA) with breath-by-breath gas exchange analysis (600USB CPX, ZAN Messgeräte GmbH, Germany).

A standard 12-lead electrocardiogram (ECG) and BP measurements (obtained with a mercury sphygmomanometer) were taken at baseline, at the end of each stage, at peak exercise, and at 1, 3, 5 and 10 min during the recovery period. A 3-lead ECG was monitored continuously before, during, and for 10 min after the exercise.

Cardiopulmonary variables: oxygen uptake (VO2, ml/min), carbon dioxide production (CO2, ml/min), and ventilation (VE, L/min) were measured continuously with breath-by-breath analysis. Exercise was considered adequate if the respiratory gas exchange ratio (VCO2/VO2) exceeded the value 1.0. The peak oxygen uptake per kilogram body weight (peak VO2, ml·kg⁻¹·min⁻¹) was defined as the highest VO2 level achieved during the final 30 s of the exercise test.

The following variables were assessed: exercise duration (s), distance (m), HR at rest and at peak exercise, double product (mmHg/min), that is, the product of HR and systolic BP at rest and at peak exercise, peak VO2, VO2 at the ventilatory anaerobic threshold (VO2AT), the efficiency of ventilation described by the slope VE/VCO2 and oxygen uptake during 1 cardiac cycle or oxygen pulse (VO2/HR, ml/beat).
Static Exercise (Handgrip)

Handgrip was performed in the sitting position at 30% of maximal voluntary contraction for 3 min. During the test, the following variables were monitored: BP, HR and stroke volume (SV), which was determined by impedance cardiography. The system allows for the off-line, beat-to-beat evaluation of SV and HR. Cardiac output (CO) was calculated as a product of SV and HR. A detailed description of the program for automatic determination of hemodynamic parameters was previously described and verified in various physiological tests.

Total peripheral resistance (TPR) was calculated by dividing mean BP by CO. Before and at the end of the third min of the test, blood samples for plasma concentrations of catecholamines, endothelin-1 and NO were taken from the antecubital vein of the non-exercising arm.

Statistical Analysis

The analysis was performed using SAS statistical software (version 8.2; Cary, NC, USA). Data were expressed as mean±SD or as percentages. Variables were compared using the Student’s t-test or analysis of variance for normally distributed variables, as tested by the Shapiro-Wilk test, and for other continuous variables, the Kruskal-Wallis test was used, followed either by the Mann-Whitney or the Wilcoxon rank test, as appropriate. Comparisons for the discrete variables between groups were performed using the chi-square test. Correlations were determined with Pearson’s or Spearman’s correlation test as appropriate. A P value <0.05 was considered statistically significant.

Results

Of 120 clinically eligible patients, 2 patients discontinued the study within 4 weeks of randomization (1 in each group) because of commuting problems.

Table 1 presents the demographic and clinical characteristics of the population studied. The 2 groups did not differ significantly in terms of age, coronary risk factors (including hypertension, smoking status, body mass index), history of angina, distribution of CAD at angiography, the number of bypassed vessels (the left internal mammary artery was used in all patients), left ventricular ejection fraction on echocardiography, and physical capacity.

In addition, all patients received standardized medication including β-blocker, angiotensin-converting enzyme inhibitor or angiotensin II receptor’s blocker, aspirin and statin, and none received nitrates or diuretics. As a result of this treatment, the serum lipid profile (total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides) and glucose levels in both groups were well controlled as evidenced by the fact that they remained within normal limits at entry and during the study (Table 2).

A 6-week of dynamic training resulted in a significant decrease in plasma levels of inflammatory markers, such as hsCRP, leucocyte and platelet count, erythrocyte sedimentation rate, fibrinogen and IL-6 (Table 2). Moreover, the HDL/cholesterol ratio was significantly higher and the LDL concentration was lower in the training group comparing with controls.

Table 3 shows the influence of a 6-week of dynamic training on the physical capacity in patients studied. Although exercise duration and distance increased in both study groups,
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Table 2. Effect of Dynamic Training on Coronary Risk Factors and Markers of Systemic Inflammation in Both Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Control (n=59)</th>
<th>P value</th>
<th>Training (n=59)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.9±3.0</td>
<td>28.2±3.2</td>
<td>NS</td>
<td>27.4±2.7</td>
</tr>
<tr>
<td>WHR</td>
<td>1.04±0.05</td>
<td>1.04±0.06</td>
<td>NS</td>
<td>1.0±0.14</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>4.1±0.9</td>
<td>4.2±1.1</td>
<td>NS</td>
<td>3.8±0.75</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.23±0.26</td>
<td>1.21±0.26</td>
<td>NS</td>
<td>1.22±0.26</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>2.6±0.83</td>
<td>2.6±0.87</td>
<td>NS</td>
<td>2.3±0.7</td>
</tr>
<tr>
<td>HDL/cholesterol ratio (%)</td>
<td>30.7±7.6</td>
<td>29.4±7.7</td>
<td>NS</td>
<td>32.9±6.8</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.46±0.76</td>
<td>1.57±0.9</td>
<td>NS</td>
<td>1.35±0.59</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.2±0.7</td>
<td>5.2±0.6</td>
<td>NS</td>
<td>5.1±0.7</td>
</tr>
<tr>
<td>Fibrinogen (g/L)</td>
<td>4.08±1.17</td>
<td>4.17±1.37</td>
<td>NS</td>
<td>3.8±1.35</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>0.24±0.27</td>
<td>0.30±0.61</td>
<td>NS</td>
<td>0.39±0.47</td>
</tr>
<tr>
<td>Leucocyte count (×10⁹/L)</td>
<td>7.0±1.6</td>
<td>7.1±1.8</td>
<td>NS</td>
<td>7.2±1.98</td>
</tr>
<tr>
<td>Platelet count (×10⁹/L)</td>
<td>209.3±50.7</td>
<td>200.5±47.8</td>
<td>NS</td>
<td>201.9±48.8</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>10.9±6.9</td>
<td>11.3±10.9</td>
<td>NS</td>
<td>10.8±10.63</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>2.6±1.79</td>
<td>2.7±2.27</td>
<td>NS</td>
<td>3.1±2.52</td>
</tr>
</tbody>
</table>

All values are presented as mean±SD.
HDL, high-density lipoprotein; LDL, low-density lipoprotein; HDL/cholesterol ratio, relationship between HDL and total cholesterol; hsCRP, high sensitive C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin-6. Other abbreviations see in Table 1.

*P<0.05, **P<0.01 changes of variables between groups.

Table 3. Results of the Cardiopulmonary Exercise Tests in the Study Groups

<table>
<thead>
<tr>
<th></th>
<th>Control (n=59)</th>
<th>P value</th>
<th>Training (n=59)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration (s)</td>
<td>775.2±100.6</td>
<td>802.1±118.9</td>
<td>&lt;0.001</td>
<td>745.6±106.9</td>
</tr>
<tr>
<td>Distance (m)</td>
<td>692.6±151.3</td>
<td>749.0±152.3</td>
<td>&lt;0.01</td>
<td>657.3±134.3</td>
</tr>
<tr>
<td>HR at rest (min⁻¹)</td>
<td>65.6±9.7</td>
<td>65.2±8.2</td>
<td>NS</td>
<td>67.4±10.9</td>
</tr>
<tr>
<td>Max HR (min⁻¹)</td>
<td>123.8±16.9</td>
<td>126.3±15.2</td>
<td>NS</td>
<td>122.0±14.7</td>
</tr>
<tr>
<td>DP at rest (mmHg/min×100)</td>
<td>76.9±14.7</td>
<td>78.5±13.7</td>
<td>NS</td>
<td>78.2±14.5</td>
</tr>
<tr>
<td>Max DP (mmHg/min×100)</td>
<td>207.4±49.8</td>
<td>216.3±47.2</td>
<td>NS</td>
<td>197.9±41.5</td>
</tr>
<tr>
<td>Peak VO₂ (ml·kg⁻¹·min⁻¹)</td>
<td>24.7±4.3</td>
<td>25.8±5.1</td>
<td>NS</td>
<td>24.3±4.5</td>
</tr>
<tr>
<td>VO₂ AT (ml·kg⁻¹·min⁻¹)</td>
<td>22.6±4.3</td>
<td>23.1±4.9</td>
<td>NS</td>
<td>22.5±4.2</td>
</tr>
<tr>
<td>VE/VO₂ slope</td>
<td>29.5±5.6</td>
<td>29.0±4.8</td>
<td>NS</td>
<td>29.1±4.0</td>
</tr>
<tr>
<td>VO₂/HR (ml/beat)</td>
<td>16.9±3.4</td>
<td>17.1±3.4</td>
<td>NS</td>
<td>16.6±3.4</td>
</tr>
</tbody>
</table>

All values are presented as mean±SD.
HR, heart rate; max HR, HR at peak exercise; DP, double product, that is, product of HR and systolic blood pressure; max DP, DP at peak exercise; VO₂ AT, VO₂ at ventilatory anaerobic threshold; VE/VO₂ slope, carbon dioxide production per unit time or ventilatory equivalent for CO₂; VO₂/HR, oxygen uptake during 1 cardiac cycle or oxygen pulse. Other abbreviations see in Table 1.

the objective indices of physical capacity (peak VO₂, VO₂ AT, VE/VO₂ slope and VO₂/HR) improved significantly only in trained patients.

Training did not affect the maximal voluntary force of handgrip (624±118 vs 638±192 newtons, P=NS, before and after training, respectively). Similar values were obtained in the control group in the initial and final tests (624±118 vs 630±214 newtons, P=NS, respectively).

Hemodynamic data obtained during static exercise are shown in Figures 1 and 2. There were no significant differences in all analyzed cardiovascular indices at initial tests between the 2 groups. The handgrip caused increases in HR, systolic and diastolic BP in both groups (Figure 1). These changes were significantly lower in the final tests in the training group compared with controls. Importantly, in the training group, SV and CO increases during the final tests were greater than that in the control group (by 13% and 15%, P<0.05, respectively) (Figure 2).

Moreover, the handgrip-induced increases in TPR during the final tests were significantly lower in trained patients than in controls (14% vs 27%, P<0.01).

Figure 3 demonstrates plasma hormone concentrations at rest and at the end of handgrip in both study groups. Interestingly, at the end of the study, a significant increase in the plasma NO level in the third min of handgrip was observed only in the training group (46% vs 14% in controls, P<0.01). Moreover, although handgrip caused significant increases in the concentrations of noradrenaline and adrenaline at the end of the initial and final handgrip in both study groups, the increase in noradrenaline during the final test was significantly lower in trained patients comparing with controls (11% vs 20%, P<0.05). The changes in endothelin-1 plasma concentration induced by handgrip did not differ significantly between the groups. This suggests that in our optimally treated
post-CABG patients, a 6-week training program resulted in a lower pressor response during handgrip performed at the end of the study.

Of note, there were no significant correlations between the handgrip-induced changes in the plasma neurohormones (noradrenaline, adrenaline, NO, endothelin-1) and A hemodynamic parameters (systolic BP, MBP, TPR and CO) in trained vs untrained post-CABG patients.

The health status was stable in all patients during the study, and in none of them were there any adverse effects of exercise training observed.

**Discussion**

The major finding of our study is that in optimally treated post-CABG patients with preserved left ventricular function, a 6-week supervised dynamic training on a cycloergometer had beneficial effects on: (1) hemodynamic and neurohormonal responses to static exercise (handgrip); and (2) inflammatory risk factors in comparison to untrained controls.

Handgrip is an isometric type of exercise known to provoke sympathetetic activation, which results in an increase in HR, CO, TPR and both systolic and diastolic BP. In our study, handgrip was used as a provocative test to examine whether short-term dynamic training had any impact on hemodynamic and neurohormonal responses to stimuli such as static exercise in optimally treated post-CABG patients. We found that handgrip-enhanced HR, BP and the TPR during the final tests were significantly lower in trained patients than in controls. Moreover, only in the training group did SV and CO increase during the final tests.

Our findings suggest that training-induced consequences of cardiac adaptation during handgrip might be related to a slower HR and less pronounced peripheral vasoconstriction. This concept is supported by the fact that at the end of the study, a significant increase in plasma NO during handgrip
occurred only in the training group. Furthermore, the increase in noradrenaline during the final handgrip was significantly lower in trained patients compared with controls. The mechanism of this favorable neurohormonal response during handgrip in trained patients is unclear. We did not find any significant correlations between Δ neurohormones and Δ hemodynamic indices in trained vs untrained post-CABG patients, showing that the mechanism of the beneficial response in trained patients is more complex and might be related to the advantageous adaptive changes in the circulation induced by regular exercise over time.

As expected, a significant increase in such variables as peak VO₂, and oxygen pulse measured during CPET, which are thought to be related to CO and SV, respectively, was observed only in trained patients.

In addition, we found that dynamic training on a cycle-ergometer not only improved the functional capacity, as evidenced by a significant increase in peak VO₂, but also exerted a pronounced effect on systemic inflammation. We found a significant decrease in plasma levels of several such inflammatory markers as hsCRP, IL-6, and fibrinogen, but only in trained post-CABG patients. It should be emphasized that baseline values of these markers were in the range, which according to the assay’s manufacturer were considered normal.

Importantly, all patients had relatively similar age and physical capacity, were on a low-fat diet and on standardized therapy, which included oral aspirin, a β-blocker, an angiotensin-converting enzyme inhibitor, and a statin. Furthermore, all of them had comparable baseline plasma levels of lipids, glucose, cardiovascular and inflammatory markers. Taken together, training-induced anti-inflammatory stimulus was of sufficient intensity, although our patient population was relatively healthy and thus less likely to respond to additional therapy.

It is noteworthy that the influence of short-term dynamic training on inflammatory markers in post-CABG patients has not been studied to date. Our findings are particularly important because stable post-CABG patients might have coronary artery plaques related to chronic inflammation. It has been suggested that this process, which involves the vessel wall, might, at least partially, be responsible for graft dysfunction, and influence the long-term outcome after CABG.

Although, plasma levels of inflammatory markers in our stable post-CABG patients remained within normal limits as in other studies with stable CAD patients, regular dynamic training can still decrease the levels of inflammatory markers. Thus, we can only hypothesize that the additive anti-inflammatory effect of dynamic training might contribute to diminishing atherosclerotic degeneration of vessel grafts in the future. Further studies are needed to confirm the long-term clinical use of anti-inflammatory properties of exercise therapy in the secondary prevention and treatment of patients after CABG.

Interestingly, in comparison with the pretreatment values, at the end of our study the levels of traditional cardiovascular disease risk factors such as body mass index, glucose and lipids, except for the HDL-cholesterol/total cholesterol ratio in trained patients, did not change significantly in either group. As mentioned previously, it is unlikely to expect that including low-risk patients in a short-term training program would result in large reductions in factors that were already within

![Figure 3. Plasma catecholamine, endothelin-1 and nitric oxide concentrations at rest (R) and at the end of static exercise (Ex.) in the control and training groups. Values are presented as mean±SD. Yellow bars—initial tests, red bars—final tests (after 6 weeks). *P<0.05, **P<0.01, significant differences between values obtained before and at the end of the third min during the final test; #P<0.05, ##P<0.01, significant differences between groups during the final test.](image)
a normal range.

This is the first study to show that a 6-week dynamic training on a bicycle ergometer in post-CABG patients with preserved left ventricular function, who are already under optimal treatment, had the potential to alter hemodynamic and neurohormonal responses to handgrip. These findings are clinically important because static efforts are very common in everyday activity. Moreover, resistive trainings of small muscle groups are increasingly included in the comprehensive training programs of cardiac rehabilitation patients.

Study Limitations

The results of this study can be applied to optimally treated groups of patients after CABG, who are without left ventricular systolic dysfunction. Women were not included because the reliability of the stress test in women is lower than that of men.

Moreover, cardiac function during handgrip was determined only non-invasively by an automatized impedance cardiography method, which allows for the automatic evaluation of SV and HR.

Conclusion

The present study demonstrated that a 6-week dynamic training program, consisting of leg cycling, in post-CABG patients with preserved left ventricular function, favorably changed hemodynamic and neurohormonal responses to handgrip and resulted in a significant improvement of cardiovascular fitness and inflammatory state.

Acknowledgment

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References