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Combined Cardiopulmonary Exercise Testing and $^{99m}$TC Sestamibi Myocardial Imaging in Trained vs Untrained Patients with Coronary Artery Disease

E. Klainman$^{1,2}$, H. Klein$^1$, I. Rosenberg$^2$, A. Yarmulovsky$^2$, R. Harduf$^3$, G. Fink$^2$

Background: The benefit of exercise training in patients (pts) with coronary artery disease (CAD) is widely conceptual while mentioning several improving systems. Methods: Cardiopulmonary exercise test (CPET) parameters and simultaneous evaluation of myocardial ischemia were performed in 15 trained and 20 untrained pts with CAD and 9 control subjects without coronary disease. The degree of ischemia was evaluated in all 44 subjects, using a $^{99m}$tscastamibi myocardial perfusion imaging carried out simultaneously with the CPET. Results: Peak oxygen consumption (peak-V.O2) was significantly higher ($p < 0.001$) and the ischemia score was significantly lower ($p < 0.001$) in the trained pts (1989 ± 422 ml/min and 0.8 ± 0.65, respectively) than in untrained pts (1608 ± 296 ml/min and 1.79 ± 0.95, respectively). The peak oxygen pulse (peak-O2-P) was significantly higher (139 ± 29 % vs 94 ± 11 % of predicted values; $p < 0.001$) and the decrease in peak heart rate (peak-HR) was also more marked in the trained group (70 ± 11 % vs 84 ± 9 % of predicted values; $p < 0.001$). Conclusion: The improvement in ischemia score in the trained pts correlates with increased stroke volume (related to the O2-P) together with the concomitant reduction in peak-HR, while allowing even higher cardiac output in these pts. Such an effect is metabolically energy-efficient for the ischemic myocardium and it is sufficient to explain the improvement in cardiopulmonary function in CAD.

Key words: cardiopulmonary exercise testing, sestamibi myocardial imaging, training effect, coronary artery disease

Several studies, among many others, have confirmed the overall benefit of physical activity in reducing the risk of coronary artery disease (CAD) [1, 2]. Other studies have shown specific benefits of exercise training in CAD patients like improvement of endothelial dysfunction without [3, 4] and with CHF [5], effect on C-reactive protein values [6] and other cytokine activity [7]. It has been established that exercising at the heart rate (HR) achieved at the ventilatory anaerobic threshold (VAT) results in a favorable training effect [8]. This concept was supported by our studies as well [9–11]. However, the mechanism by which exercise training at the VAT level exerts its beneficial effect in CAD patients remains unclear: does it enhance the development of collateral coronary blood supply to the ischemic myocardium? Or can the improvement in cardiopulmonary function be readily explained by other mechanisms such as a more cost-effective metabolic-physiologic demand and supply balance?

According to the Fick formula [12, 13], oxygen consumption (V.O2) equals cardiac output (CO) multiplied by the difference in arterial (a) and venous (v) oxygen content:

$$\text{V.O2} = \text{SV} \times \text{HR} \times (a-v) \times \text{O2 content}$$

Accordingly, oxygen-pulse (O2-P), which is simply V.O2 divided by HR, is directly related to SV. It follows that if O2-P is significantly increased by exercise training, it means that exercise training improves SV. This could theoretically be induced by improved myocardial perfusion (e.g., by augmented collateral circulation) but so far there has been a paucity of definite proof that exercise training indeed exerts such a beneficial effect on myocardial oxygen supply.

Alternatively, the increase in SV, especially if accompanied by a decrease in HR at VAT, could simply reflect improved and more effective myocardial V.O2 as a result of training which may be accompanied by objective evidence of improved myocardial ischemia. This could occur simply as a result of a significant decrease in exercise HR for example.

In the present study, we evaluated and compared the functional cardiopulmonary exercise test (CPET) indices in trained and untrained CAD patients with the degree of ischemia observed by $^{99m}$tscastamibi myocardial perfusion imaging (MBI-SPECT), while using the same exercise testing for both tests. We tested the theory that a decrease in myocardial oxygen demand could explain the improved functional capacity seen after cardiopulmonary training in chronic CAD patients, irrespective of its possible effects on collateral blood flow.

Material and Methods

Patients

Forty-four men aged 40–83, mean 62 ± 12 years with a recent coronary angiogram were included in the study. They were divided into 3 age-matched groups as follows:

- Group I: Nine pts with normal coronary arteries at coronary angiography (control group).
- Group II: Twenty pts with significant 1–3-vessel disease who did not participate in any exercise training program (untrained group).
- Group III: Fifteen pts with significant 1–3-vessel disease, who had completed a 3–6-month supervised, telemeter-monitored, exercise training program prescribed according to the HR at the VAT (trained group). All 35 CAD pts had chronic CAD, without any previous acute coronary events. All had normal left ventricular (LV) function (LVEF > 50 %) by multigated acquisition angiography (MUGA) study or by LV angiography.

All 44 participants underwent a CPET together with a MIBI-SPECT examination using standardized techniques. A single exercise test was used for both studies. Betablockers and calcium channel antagonists were stopped 24 hours before testing.
The study protocol was approved by the local ethics committee, and written informed consent was obtained from each participant in the study.

**Cardiopulmonary Exercise Test**

An upright symptom-limited test was performed on an electronically braked cycle ergometer (Ergoline 800). Exercise was initiated after a 3-minute rest and 2 minutes of free pedaling at a rate of 60 rpm. The effort was then progressively increased by 10–20 Watt/min until the predefined end-point was reached, namely, symptoms, volitional fatigue, or attainment of the target HR. Cardiopulmonary data were collected by an online metabolic unit (CPX MedGraphics, Minnesota, USA).

Pts breathed through a low-resistance, two-way valve (Hans Rudolph, Missouri, USA) connected to the expiratory limb. The breath-by-breath signals were integrated by a computer to yield 30-sec and averages of HR, minute ventilation, VO\(_2\), VCO\(_2\), and O\(_2\)-P (VO\(_2\)/HR). VAT was defined as the point at which the ventilatory equivalent of O\(_2\) (VE/V.O\(_2\)) increased in the absence of a similar increase in the ventilatory equivalent of CO\(_2\) (VE/V.CO\(_2\)), as described by Beaver et al [14]. Blood pressure was measured at rest, every 2 minutes, and at peak exercise.

**MBI-SPECT Protocol**

MBI myocardial perfusion tomography was performed with a same-day “rest-stress” imaging protocol [15]. The first myocardial perfusion imaging was done at rest, 1 hour after injection of MIBI 7–8 mc. The second imaging was done 1–2 hours later, after exercise and additional injection of MIBI 21–22 mc at peak exercise. Tomographic imaging acquisition was performed over a 180-degree arc, from the –45-degree right anterior oblique to the +135-degree left posterior oblique with an S-P-4 digital camera (Elscint Ltd, Haifa, Israel) fitted with an all-purpose collimator. The MIBI images were interpreted by consensus of two experienced observers blinded to the clinical data and the other diagnostic studies. The degree of ischemia was scored on a 4-point scale: 0 – none; 1 – mild; 2 – moderate; 3 – severe but reversible. Stress image defects that showed partial or complete resolution on corresponding rest images were considered “reversible ischemia”.

**Statistical Analysis**

Mean ± standard deviation was calculated for each parameter. The paired Student’s t-test was used for intergroup comparison. P values < 0.05 were considered statistically significant.

**Results**

The basic data and summary of results for all 3 groups are shown in Table 1, and the extent of disease in the trained and untrained pts is shown in Table 2. There was an almost equal distribution of 1-, 2- and 3-vessel disease within groups II and III with no significant difference in extent of disease between the groups (Table 2). Significantly less ischemia was observed in the trained pts (group III) in comparison to the untrained pts is shown in Table 2. There was an almost equal distribution of 1-, 2- and 3-vessel disease within groups II and III with no significant difference in extent of disease between the groups (Table 2). Significantly less ischemia was observed in the trained pts (group III) in comparison to the untrained pts (group II) (0.8 ± 0.56 vs 1.79 ± 0.95; p < 0.001), as demonstrated also in Figure 1, along with a significantly greater peak-VO\(_2\) (1989 ± 422 vs 1608 ± 296 ml/min; p < 0.001). Since peak-VO\(_2\) equals peak-O\(_2\)-P × HR, as mentioned above, a highly significant increase in peak-O\(_2\)-P was observed in the trained vs the untrained group (139 ± 29 % vs 94 ± 11 % of predicted values; p < 0.001) concomitantly with a significantly lower peak-HR (70 ± 11 % vs 84 ± 9 % of predicted values; p < 0.001).

Peak-VO\(_2\) and O\(_2\)-P were not significantly different in the trained group (group III) vs the control group (group I). The comparison of the relationship among the peak-VO\(_2\), peak-O\(_2\)-P and peak-HR within the 3 groups is demonstrated in Figure 2.

**Discussion**

Exercise is a highly valuable non-pharmacological treatment for pts with chronic stable angina. Exercise training reduces myocardial ischemia, and, on the clinical level, reduces the frequency of angina attacks while improving functional capacity and long-term outcomes [16]. As regular exercise has been shown to improve myocardial perfusion and to retard disease progression in pts with stable CAD and even with ischemic cardiomyopathy [17], Hambrecht et al [18] conducted a randomized study to compare the effects of exercise

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**Table 1. Basic data and summary of results.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yrs)</th>
<th>No of occluded vessels</th>
<th>Ischemic degree (score)</th>
<th>Peak-VO(_2) (ml/min)</th>
<th>Peak-O(_2)-pulse (%pred.)</th>
<th>Peak-HR (%pred.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>64 ± 7</td>
<td>0</td>
<td>0</td>
<td>1711 ± 536</td>
<td>125 ± 24*</td>
<td>89 ± 77</td>
</tr>
<tr>
<td>Group II</td>
<td>61 ± 8</td>
<td>0</td>
<td>0</td>
<td>1608 ± 296</td>
<td>94 ± 11†</td>
<td>84 ± 9†</td>
</tr>
<tr>
<td>Group III</td>
<td>64 ± 9</td>
<td>1</td>
<td>1</td>
<td>1989 ± 422</td>
<td>139 ± 29</td>
<td>70 ± 11</td>
</tr>
</tbody>
</table>

* p < 0.05 group I vs group II; †p < 0.01 group I vs group III; ‡p < 0.001 group II vs group III.

**Figure 1. Comparison of number of occluded coronary vessels and scoring of the ischemic degree (as evaluated by Tc99m-Sestamibi test) between groups II (untrained) and III (trained).**

**Figure 2. Extent of coronary disease on angiography in trained and untrained patients.**

<table>
<thead>
<tr>
<th>Group</th>
<th>1-vessel disease</th>
<th>2-vessel disease</th>
<th>3-vessel disease</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>7 (35 %)</td>
<td>7 (35 %)</td>
<td>6 (30 %)</td>
<td>20 (100 %)</td>
</tr>
<tr>
<td>Group II</td>
<td>6 (40 %)</td>
<td>4 (27 %)</td>
<td>5 (33 %)</td>
<td>15 (100 %)</td>
</tr>
</tbody>
</table>
training versus percutaneous coronary intervention with stenting on clinical symptoms, angina-free exercise capacity, myocardial perfusion and cost-effectiveness. They concluded that a 12-month program of regular physical exercise in pts with stable CAD resulted in increased event-free survival and exercise capacity at lower costs, notably owing to reduced rehospitalization and repeat revascularizations.

What Is the Contribution of This Study?
What has not become clear from the past studies is the dominant mechanism that underlies the cardiovascular improvement induced by an exercise program. Is the improvement mainly dominated by enhanced myocardial blood flow (by increased coronary collateralization for example, as well as by augmentation in endothelial function) or is it due to decreased myocardial oxygen demand and improved metabolic cost-effect balance? (the improved ischemic burden evidenced by perfusion studies is compatible with either of these possibilities.)

The present study does not deny the former possibility (increased myocardial perfusion) since it does not address this issue at all. However, the contribution of this study is in showing that the reduced ischemic burden seen on perfusion studies can be attributed to a substantial degree, if not completely, to the improved metabolic-physiologic state of the myocardium that accrues from exercise training.

We indeed show in the present study that SV (as indicated by O2-P) is significantly higher in CAD patients after a 3–6-month threshold by gas exchange. J Appl Physiol 1986; 60: 2020–7.

References:
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