Increased Arteriovenous Oxygen Difference
After Physical Training in Coronary Heart Disease

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SUMMARY
A preliminary study of 12 male patients (mean age, 47.8 years) with coronary heart disease (six with angina pectoris and six with prior myocardial infarction but without angina) was conducted according to a common protocol in Seattle, Washington, and Louvain, Belgium. Maximal oxygen intake (\(\dot{V}_{O_2} \text{max}\)) and hemodynamic studies at rest and at two or three levels of submaximal exercise in the upright position were obtained before and after a 3-month physical training program that involved three sessions of 45 min/week. \(\dot{V}_{O_2} \text{max}\) increased 22.5% (\(P < 0.0001\)) with physical training. Changes in maximal heart rate occurred in the patients with angina (+8.4%) but not in those without angina (+0.8%). At rest and at each submaximal exercise, heart rate, mean blood pressure, and cardiac output decreased after training, whereas stroke volume was unchanged and arterio-mixed venous oxygen (A-Vo\(_2\)) difference increased. The pressure-rate product and the left ventricular work decreased after training. The classic posttraining bradycardia was compensated not by a higher stroke volume but by an increased A-Vo\(_2\) difference which resulted from both a higher arterial oxygen content and an increased peripheral oxygen extraction. The latter was more apparent when exercises of the same relative intensity were compared.

Thus, benefits with physical training in coronary patients result at submaximal exercise level from enhanced arterial oxygen content and peripheral extraction and secondarily from lower hemodynamic stress on ischemic myocardium. Increased maximal A-Vo\(_2\) difference probably explains most of the increase in \(\dot{V}_{O_2} \text{max}\) with physical training in coronary patients not limited by angina pectoris.

**Additional Indexing Words:**
Maximal oxygen intake  
Arterial oxygen content  
Cardiac output  
Pressure-rate product  
Peripheral oxygen extraction

**P**hysical training is now recommended in the rehabilitation of ambulatory patients with coronary heart disease as there is increasing evidence of its beneficial effects. Heart rate at rest and at any given submaxi-

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### Clinical Data

<table>
<thead>
<tr>
<th>No.</th>
<th>Patient</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Resting blood pressure (mm Hg)</th>
<th>Medical history</th>
<th>Heart volume (ml)</th>
<th>Delay between MI and onset of training</th>
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<tbody>
<tr>
<td>1</td>
<td>A.D.</td>
<td>34</td>
<td>181</td>
<td>94</td>
<td>120/78</td>
<td>MI May 1969 and November 1969. Angina pectoris. Selective coronary arteriography showed three vessels diseased.</td>
<td>1277</td>
<td>4 months</td>
</tr>
<tr>
<td>2</td>
<td>B.W.</td>
<td>50</td>
<td>170</td>
<td>79</td>
<td>116/80</td>
<td>MI October 1969. Angina pectoris.</td>
<td>727</td>
<td>6 1/2 months</td>
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<tr>
<td>3</td>
<td>B.C.</td>
<td>42</td>
<td>173</td>
<td>75</td>
<td>110/85</td>
<td>MI December 1969. Angina pectoris.</td>
<td>737</td>
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<tr>
<td>4</td>
<td>K.A.</td>
<td>46</td>
<td>159</td>
<td>63</td>
<td>120/90</td>
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<td>8 months</td>
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<td>5</td>
<td>K.W.</td>
<td>38</td>
<td>184</td>
<td>70</td>
<td>110/70</td>
<td>MI September 1969.</td>
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<td>6</td>
<td>R.A.</td>
<td>61</td>
<td>177</td>
<td>65</td>
<td>130/60</td>
<td>MI September 1965. Right bundle-branch block.</td>
<td>665</td>
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<tr>
<td>7</td>
<td>S.G.</td>
<td>68</td>
<td>169</td>
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<td>130/85</td>
<td>MI 1963 and May 1969. Angina pectoris.</td>
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<td>8</td>
<td>T.C.</td>
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<td>89</td>
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<td>MI July 1962 and January 1967. Selective coronary arteriography showed three vessels diseased.</td>
<td>1074</td>
<td>3 years, 4 months</td>
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<td>9</td>
<td>C.J.*</td>
<td>44</td>
<td>163</td>
<td>66</td>
<td>120/80</td>
<td>MI January 1970.</td>
<td>764</td>
<td>3 months</td>
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<tr>
<td>10</td>
<td>D.A.*</td>
<td>54</td>
<td>172</td>
<td>82</td>
<td>140/80</td>
<td>Exercise angina pectoris since June 1969.</td>
<td>—</td>
<td>—</td>
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<tr>
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<td>171</td>
<td>73</td>
<td>135/90</td>
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<td>4 months</td>
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<tr>
<td>12</td>
<td>L.J.*</td>
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<td>76</td>
<td>140/80</td>
<td>MI February 1970.</td>
<td>1011</td>
<td>2 1/2 months</td>
</tr>
</tbody>
</table>

Abbreviation: MI = myocardial infarction.

*These cases were studied in Louvain.
mal work load is usually decreased after physical training. This lower heart rate has to be compensated by either a larger stroke volume or a wider arteriovenous oxygen (A-V\textsubscript{O\textsuperscript{2}}) difference. Which of these mechanisms is effective in coronary heart disease is uncertain since A-V\textsubscript{O\textsuperscript{2}} difference has been reported as increased\textsuperscript{1} or unchanged\textsuperscript{2,3} after physical training.

An international cooperative study was planned, under the auspices of the Scientific Council on Cardiac Rehabilitation, International Society of Cardiology, to clarify effects of physical training on coronary patients. The study was designed to determine the changes in maximal oxygen intake (“V\textsubscript{O\textsuperscript{2} max}” with physical training and to measure the hemodynamic changes by the direct Fick principle at rest and at several submaximal exercise levels. Initial results from two participating centers (Louvain, Belgium, and Seattle, Washington) are presented at this time.

**Material**

Twelve male patients (ranging in age from 34 to 68 years, with a mean age of 47.8 years) with coronary heart disease had “V\textsubscript{O\textsuperscript{2} max}” determinations and hemodynamic studies before and 3 months after the onset of a physical training program (table 1). Six of these patients had typical exercise angina pectoris, and six others without angina had previous acute myocardial infarction. Two of the angina patients (no. 1 and 3, table 1) were taking beta-blocking agents, but the doses remained unchanged during the complete study. Patients with hypertensive disease (resting blood pressure 160/90 mm Hg), clinically manifest heart failure, or ventricular aneurysm were excluded from the study. None received digitalis. Informed consent after appropriate explanations was obtained from each subject before he entered the study.

**Methods**

A common protocol was used in Louvain and Seattle except for minor differences in the procedures which will be mentioned. Each patient had a clinical examination, resting 12-lead ECG, and upright chest X-ray for appraisal of heart volume.

**Maximal Oxygen Intake**

“V\textsubscript{O\textsuperscript{2} max}” was measured in a single test of progressive exercise. A multistage treadmill test was used in Seattle,\textsuperscript{4,5} while a multistage bicycle exercise test (with an initial work load of 10 w and successive increments of 10 w every minute) was performed in Louvain.\textsuperscript{6} Exercise was continued until the patient reached a self-determined limit of maximally tolerable fatigue, dyspnea, leg weakness, or angina pectoris. The “V\textsubscript{O\textsuperscript{2} max}” was measured several days before the hemodynamic studies in Louvain (pre- and posttraining) and in Seattle (pretraining study); in Seattle the posttraining “V\textsubscript{O\textsuperscript{2} max}” was measured 3–4 hr after the hemodynamic study in order to reduce the patient’s time lost from gainful employment.

Heart rate and ECG were monitored from a bipolar ECG lead (Seattle) or from precordial V\textsubscript{1}, V\textsubscript{5}, or V\textsubscript{6} (Louvain); S-T-segment depression was never a reason for stopping exertion. No test had to be interrupted for a significant arrhythmia. Continuous magnetic tape recordings of the bipolar lead and Frank leads (X, Y, Z) were obtained in Seattle and later analyzed by computer averaging technique.\textsuperscript{7} Maximal heart rate was measured during the last 30 sec of the test.

One-minute samples of expired air were collected through a low resistance open circuit during the last 3 to 4 min of the test. Oxygen content of expired air samples was measured with a paramagnetic oxygen analyzer (Beckman or Servomex), and volume was measured with a dry Gasmeter (Parkinson and Cowan or American Meter Co.). Maximal oxygen intake (STPD) was expressed in ml O\textsubscript{2}/kg X min.

**Hemodynamic Studies**

A polyvinyl catheter (0.9 mm inner diameter, 1.3 mm outer diameter) was introduced percutaneously into the basilic vein and floated into the pulmonary artery. A Teflon catheter-needle was inserted into the brachial or radial artery of the same arm (Seattle), and in Louvain a polyethylene radiopaque catheter was introduced into the brachial artery by the Seldinger technique and advanced into the ascending aorta. The catheters were connected to a Statham P23 Db transducer; zero level was the fourth intercostal space in the sitting position. The ECG was monitored as during maximal oxygen uptake determination.

The patients sat on a bicycle ergometer—Fleisch (Louvain) or Monark (Seattle)—where the resting measurements were made. Two exercise periods of 7-min duration each were separated by a 30-min rest period; the two work loads corresponded to 45% and 75% of the pretraining “V\textsubscript{O\textsuperscript{2} max}.” In some cases (Seattle) a third work load at 90 ± 5% of “V\textsubscript{O\textsuperscript{2} max}” was performed during 4 to 5 min after a second 30-min rest period. The pedaling rate was 40 rpm in Louvain and 50 rpm in Seattle.
The cardiac output was measured in duplicate by the Fick principle during the last 2 min of each rest or exercise period. Expiratory gases were collected and analyzed as for the \( \dot{V}_{O_2} \text{max} \) determination. Blood samples were drawn simultaneously from the pulmonary artery and peripheral artery, and the oxygen content was determined by the Van Slyke technique. The heart rate was counted from a continuous ECG paper recording. The mean pressures were obtained by electrical integration. The ECG (bipolar and Frank leads) was recorded on magnetic tape during the hemodynamic determination (Seattle) for subsequent computer analysis.

All patients were conditioned to the experimental procedures by performing each work load for preliminary measurements of oxygen intake before the hemodynamic study.

In Louvain, the posttraining hemodynamic study was similar to the pretraining study. In Seattle the work loads utilized before training were repeated in the same way but, after 7 min of exercise and hemodynamic measurements, some patients were asked to continue exercise for 5 to 6 min longer at a slightly higher work load. Cardiac output and pressure determinations were then repeated during the last 2 min of this higher work load. This minor modification in the protocol was intended to provide additional data after training without prolonging the total duration of the study excessively.

The following indices were calculated:
(a) Pressure-rate product, in units = HR \( \times \) BP/100, where HR = heart rate and BP = mean arterial blood pressure.
(b) Peripheral vascular resistance, in units = BP/\( \dot{Q} \), where \( \dot{Q} \) = cardiac output.
(c) Pulmonary vascular resistance, in units = PA/\( \dot{Q} \), where PA = mean pulmonary arterial pressure.
(d) Left ventricular work, in units = \( BP \times \dot{Q} \).
(e) Left ventricular stroke work, in units = \( BP \times SV \), where SV = stroke volume.

### Physical Training Program

In both centers, the patients met three times a week for 45-min training sessions under medical supervision. In Seattle, the training was under direction of the professional staff of the Cardio-Pulmonary Research Institute (CAPRI), using the facilities of the Downtown Seattle YMCA gymnasium. The training consisted of six graded levels of walking, jogging, and running, and 12 calisthenics scaled from five to 15 repetitions according to the capacity of each patient. In Louvain, the training done at the University Hospital included walking, calisthenics, jogging, rowing, and bicycling at five graded levels also scaled to the capacity of each patient.

Intensity of physical training was adjusted to each individual capacity taking into account initial \( \dot{V}_{O_2} \text{max} \), heart rate during training, and subjective reactions and feelings of each patient. The training was largely submaximal, without attempt to precipitate angina pectoris; when the latter occurred, the patients used nitroglycerin for relief of pain and resumed training.

### Table 2

**Effect of Physical Training on Maximal Performances**

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Parameter</th>
<th>Before physical training*</th>
<th>After physical training*</th>
<th>Difference†</th>
<th>% change</th>
<th>( P^* )</th>
</tr>
</thead>
</table>
|                 | \( \dot{V}_{O_2} \text{max} \) & 18.59 ± 3.31 & 24.28 ± 5.14 & + 5.68 ± 1.27 & +30.6 & <0.01 &
|                 | HR              & 131.6 ± 11.1 & 142.6 ± 21.6 & +11 ± 5.4 & +8 & NS &
|                 | \( \dot{V}_E \)  & 44.7 ± 13.0 & 60.4 ± 19.3 & +15.7 ± 4.2 & +33.1 & <0.02 &
| **With angina pectoris** |
|                 | \( \dot{V}_{O_2} \text{max} \) & 27.34 ± 4.99 & 32.15 ± 4.63 & + 4.81 ± 0.84 & +17.7 & <0.005 &
|                 | HR              & 174.5 ± 10.1 & 176 ± 6.6 & +1.5 ± 3.4 & +0.8 & NS &
|                 | \( \dot{V}_E \)  & 70.7 ± 20.0 & 80.9 ± 23.2 & +10.2 ± 4.1 & +14.4 & NS &
| **Without angina pectoris** |
|                 | \( \dot{V}_{O_2} \text{max} \) & 23.0 ± 6.1 & 28.2 ± 6.2 & +5.2 ± 0.74 & +22.6 & <0.0001 &
|                 | HR              & 153.1 ± 24.5 & 159.4 ± 23.2 & +6.2 ± 3.35 & +4 & NS &
|                 | \( \dot{V}_E \)  & 57.7 ± 21.0 & 70.6 ± 23.0 & +12.9 ± 2.9 & +22.4 & <0.001 &
| **All patients** |

Abbreviations: \( \dot{V}_{O_2} \text{max} \) = maximal oxygen intake (ml/kg/min); HR = heart rate (beats/min); \( \dot{V}_E \) = ventilation (liters/min).

*Mean values = standard deviation.
†Mean values = standard error.
‡Significance of difference calculated by paired t-test.
Statistical Methods

Significances of differences were analyzed by means of the paired t-test; unpaired data were disregarded for the calculation of means.

Results

Maximal Oxygen Intake

After physical training (table 2), "\( \dot{V}_{\text{O}_2 \text{ max}} \)" was increased by 22.6% (\( P < 0.0001 \)), maximal ventilation by 22.4% (\( P < 0.001 \)), and maximal heart rate by 4% (NS). The increase in "\( \dot{V}_{\text{O}_2 \text{ max}} \)" was greater in patients with angina pectoris (+30.6%) who had lower pretraining values than in patients with healed myocardial infarction but no angina (+17.7%). Similarly, maximal heart rate was increased by 8% in angina patients, while the change was only 0.8% in patients without angina. There were no significant changes in heart volume.

All patients felt subjectively improved after the 3-month training program, and two patients limited by angina pectoris before training were free of angina at any level of exertion after the physical training period.

Hemodynamic Data

Table 3 summarizes the hemodynamic data at rest and at exercise levels corresponding to 45% and 75% of the pretraining "\( \dot{V}_{\text{O}_2 \text{ max}} \)". Data at the third exercise level (corresponding to 90% of the pretraining "\( \dot{V}_{\text{O}_2 \text{ max}} \)") obtained before and after training in only two cases were not considered separately but were included for the general calculations and in the figures.

At rest and at the two submaximal exercise levels, ventilation, heart rate, cardiac output, mean arterial pressure, and pressure-rate product were all significantly decreased while arterio-mixed venous oxygen (A-V\( \text{O}_2 \)) difference, arterial oxygen content, and oxygen pulse were significantly increased. Stroke volume, mean pulmonary artery pressure, and left ventricular stroke work were unchanged. Left ventricular work was significantly decreased during exercise. Minor changes occurred in peripheral vascular resistance and in pulmonary vascular resistance.

The individual data for heart rate, A-V\( \text{O}_2 \) difference, cardiac output, and pressure-rate product are presented in figures 1 to 4. Hemodynamic changes noted at rest and at submaximal level after physical training in patients with angina pectoris were not significantly different from those in patients without angina.

The increased A-V\( \text{O}_2 \) difference at a given submaximal level was explained primarily by increased arterial oxygen (table 3, fig. 5) content. However, peripheral oxygen extraction was also increased since the extraction coefficient (A-V\( \text{O}_2 \) difference divided by arterial oxygen content \times 100) after training rose from 30.8 to 32.3% at rest (NS), from 46.8 to 49.5% at the low exercise level (NS), and from 56.3 to 59.3% at the higher exercise level (\( P < 0.01 \)); this increase was highly significant (\( P < 0.001 \)) when all resting and exercise data were pooled.

Discussion

The major hemodynamic finding was a decreased cardiac output at rest and at submaximal exercise levels after physical training. This lower cardiac output was attended by an increased A-V\( \text{O}_2 \) difference, an unchanged stroke volume, and lower heart rate.
rate and blood pressure. Consequently the pressure-rate product and the left ventricular work at submaximal exercise were also lower after physical training.

These changes are similar to those observed by Varnauskas et al. in six coronary patients after 1 month of physical training, but very different from those reported in two other studies, which have shown an unchanged submaximal cardiac output with an increased stroke volume after physical training. Review of these reports revealed no apparent difference either in the selection of the patients or in intensity of the physical training program that could explain such divergent results. The supine position used by Frick and Katila for their hemodynamic measurements is of importance, however, because of different hemodynamic adjustments in this posture.

All the studies on the effects of physical training agree on one point, namely that resting and submaximal heart rates are lower after physical conditioning. Consequently, for any level of submaximal energy expenditure there must be a compensatory increase in stroke volume and/or A-V-O₂ difference to balance the decrease in heart rate. In normal young or middle-aged subjects, both adaptive mechanisms may be operative since the submaximal stroke volume has been reported increased or unchanged.

Unlike healthy subjects, patients with coronary heart disease compensate their lower
posttraining heart rate by an increased A-Vo2 difference rather than by an increased stroke volume. At the same submaximal level after physical training, this greater A-Vo2 difference resulted mainly from a 3.3 to 4.2% increase in arterial oxygen content. It was not possible to determine from these data whether this higher arterial oxygen content resulted from a higher arterial saturation, a higher hemoglobin content, or both. A higher hemoglobin content with a higher arterial oxygen capacity has been reported after physical training.

Whether physical training might cause an increase in stroke volume in some patients with relatively minor coronary arterial lesions as it does in normal middle-aged subjects is not clear. This hypothesis could explain some of the divergent results in the literature, but it is impossible to verify since neither coronary arteriography nor left ventriculography was utilized.

A lower cardiac output at submaximal energy expenditure raises the question of how it is distributed. Since splanchnic and renal blood flow at a submaximal level are higher in trained than in untrained subjects, the muscle blood flow for the same submaximal exertion probably is lower after physical training. A lower muscle blood flow after physical training has indeed been reported in normal young subjects and in patients with coronary heart disease.

Physical training induced a 22.6% increase in \( \text{Vo2 max} \) and a 4% increase in maximal heart rate. These changes are less marked than the 39.2% increase in \( \text{Vo2 max} \) and the 7% increase in maximal heart rate after 3 months of training reported by Kasch and Boyer. As in healthy sedentary middle-aged men, the magnitude of improvement was inversely related to the initial level of physical fitness.

---

<table>
<thead>
<tr>
<th>CO (liters/min)</th>
<th>SV (ml/beat)</th>
<th>Mean arterial pressure (mm Hg)</th>
<th>Mean pulmonary pressure (mm Hg)</th>
<th>O2 pulse (ml/beat)</th>
<th>Pressure-rate product (mm Hg/min)</th>
<th>LVW (units)</th>
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<tr>
<td><strong>At rest</strong></td>
<td></td>
<td></td>
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<tr>
<td>5.2 ± 1.1</td>
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<td>102 ± 11</td>
<td>11 ± 3</td>
<td>3.68 ± 0.76</td>
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<td>11 ± 2</td>
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<td>-0.9</td>
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<td>&lt;0.02</td>
<td>NS</td>
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<td>&lt;0.05</td>
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<tr>
<td>9.1 ± 2.0</td>
<td>88 ± 10</td>
<td>113 ± 8</td>
<td>18 ± 5</td>
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<td>7.9 ± 2.1</td>
<td>89 ± 14</td>
<td>107 ± 8</td>
<td>19 ± 4</td>
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<td>83 ± 17</td>
<td>115 ± 16</td>
<td>19 ± 8</td>
<td>7.79 ± 3.12</td>
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<td>106 ± 17</td>
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<tr>
<td>-0.9 ± 0.13</td>
<td>+1 ± 1.3</td>
<td>-8 ± 1.4</td>
<td>-0.7</td>
<td>+0.90 ± 0.12</td>
<td>-23 ± 2.3</td>
<td>-186 ± 23</td>
</tr>
<tr>
<td>-11%</td>
<td>+1.2%</td>
<td>-7.8%</td>
<td>-</td>
<td>+11%</td>
<td>-19.5%</td>
<td>-17.9%</td>
</tr>
<tr>
<td>34</td>
<td>34</td>
<td>37</td>
<td>32</td>
<td>37</td>
<td>37</td>
<td>34</td>
</tr>
<tr>
<td>&lt;0.0001</td>
<td>NS</td>
<td>&lt;0.0001</td>
<td>NS</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Circulation, Volume XLIV, July 1971
(Detry J.M., Bruce R.: Unpublished observations). The increase in maximal heart rate was confined to the patients with angina pectoris (+8%) and was not present in the patients without angina.

The data collected at the level of maximal exercise have to be interpreted with caution. Indeed, the \( \dot{V}_{\text{O}_2} \text{max} \) measured in the angina patients is a pain-limited one and, therefore, does not have the same physiologic meaning as a true \( \dot{V}_{\text{O}_2} \text{max} \) measured in a normal subject. Presumably the improvement noted after training in angina patients results mainly from their lower heart rate and blood pressure and, therefore, lower myocardial oxygen requirements during exercise. This could explain why, after physical training, they are able to perform more external work and, therefore, consume more oxygen before they are stopped by the anginal pain. Since the arterial blood pressure and the ejection time were not measured during maximal exercise, it is impossible to determine whether the angina patients were able to meet higher myocardial oxygen requirements after physical conditioning. Although the latter is suggested by their higher maximal heart rate, the ECG evidence of myocardial ischemia is often...
Influence of physical training on resting and sub-maximal values of arterial and mixed venous blood oxygen content. The intensity of the exercise is expressed in absolute values (V\textsubscript{O\textsubscript{2}} ml/min).

As suggested by the values of maximal heart rate, the "V\textsubscript{O\textsubscript{2}} max" measured before and after training in coronary patients not limited by angina probably are close approximations to the true V\textsubscript{O\textsubscript{2}} max. If the latter is true, then a 17.7% increase in this value requires explanation. Unfortunately, we did not measure hemodynamic data at maximal exercise level in this study. The only explanation we can currently offer is that the increase in "V\textsubscript{O\textsubscript{2}} max" probably resulted from an expanded A-V\textsubscript{O\textsubscript{2}} difference, since neither the maximal heart rate nor the submaximal stroke volume was significantly altered by physical conditioning.

In conclusion, the major effect of physical training in ambulatory patients with coronary heart disease was a significant decrease of heart rate and cardiac output at rest and at submaximal levels of exercise. Unchanged submaximal oxygen uptake was maintained by an increase in A-V\textsubscript{O\textsubscript{2}} difference associated with a higher arterial oxygen content and no change in mixed venous oxygen content. In contrast to responses of normal subjects, the stroke volume of these patients was not increased by training. At submaximal levels of exercise, lower heart rate and arterial blood pressure resulted in reduction of the pressure-rate product and, accordingly, of myocardial oxygen requirements. Possibly, the coronary blood supply, although still restricted by coronary heart disease, more closely approximated myocardial metabolic demands. Since ventilation also decreased, awareness of dyspnea was often diminished as well.

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References


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