Cardiovascular Mechanisms of Functional Aerobic Impairment in Patients with Coronary Heart Disease

By Robert A. Bruce, M.D., Fusako Kusumi, M.S., Manfred Niederberger, M.D., and John L. Petersen, M.D.

SUMMARY
Maximal oxygen uptake (\(V_{O2}\text{max}\)) and functional aerobic impairment (FAI) were determined by treadmill test in 42 men with coronary heart disease and in 11 slightly older healthy men. Patients were separated according to occurrence or nonoccurrence of angina with exercise. At rest and at four levels of submaximal exercise on a bicycle ergometer, cardiac output (\(Q\)), using the direct Fick principle, heart rate (HR), mean systemic and pulmonary arterial pressures, and arterial-mixed venous oxygen difference (A-V \(O_2\) D) were evaluated in relation to relative aerobic requirement (% \(V_{O2}\text{max}\)). \(Q\) was highly correlated with \(V_{O2}\), and both the level and the rate of change of \(Q\) were lower in patients with angina at all submaximal workloads. Stroke volume (SV) and HR were significantly restricted at the higher workloads. Although peripheral resistance was increased, there was no compensatory increase in A-V \(O_2\) D. Both restricted SV and reduced HR are responsible for cardiovascular components of the abnormal FAI found in patients with myocardial ischemia due to coronary arterial disease.

Additional Indexing Words:
Angina Stroke volume Coronary heart disease Maximal oxygen uptake Treadmill testing

FUNCTIONAL AEROBIC IMPAIRMENT (FAI) represents the percentage difference between functional aerobic power observed with maximal exercise testing and that expected of a healthy person of similar sex, age and habitual physical activity status. Since the FAI of ambulatory patients with cardiovascular disease can be determined from duration of exercise with a standardized multistage treadmill protocol by using a nomogram, the salient question arises as to how much restriction of stroke volume, heart rate, arterial-mixed venous oxygen difference and arterial pressure contributes to this cardiovascular impairment. Of these factors, the first two define cardiac output, the third, peripheral extraction and the fourth, the pressure available for circulatory delivery of oxygen.

This study analyzes the restrictive effects of exertional myocardial ischemia by comparing the circulatory responses to upright exercise of patients with coronary heart disease, with and without angina pectoris, with slightly older healthy subjects. The experimental design required determination of maximal oxygen uptake of each individual in order to scale four levels of submaximal exercise to physiologically comparable relative aerobic requirements.

Material and Methods
The physical and clinical characteristics of 11 healthy middle-aged men and 42 male patients with coronary heart disease (CHD) are listed in table 1. Although the patients averaged 51 ± 9 years and the normal men 55 ± 5 years, neither the ages nor the other physical characteristics showed significant differences. The study design was explained and informed consent was obtained from each individual.

The coronary patients were separated into two groups, 19 who experienced typical anginal pain on maximal exercise testing, and 23 who were limited by fatigue and dyspnea rather than chest pain. Maximal oxygen uptake was determined from the highest value.

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observed during the last 3-5 min of a multistage treadmill test of maximal exercise. Oxygen uptake (V_o2) was measured by the open-circuit method using dual analysis of Po2 in aliquots of expired air, first with and then without CO2 absorption in order to ascertain the concentrations of O2 and CO2, respiratory exchange ratio, and valid determinations of V_o2. FAI was determined from duration of this test by use of the appropriate nomograms for healthy men and those with cardiac disease. A bipolar precordial ECG lead was monitored to detect any arrhythmia or change in ST segment displacement.

Usually on another day, a Swan-Ganz catheter was positioned into a pulmonary artery by monitoring recorded pressure, and another sampling catheter was inserted by the Seldinger technique into either the radial or the brachial artery. When the subjects sat upright, mean arterial pressures (P) were recorded with transducers positioned at the level of the fourth anterior interspace. Heart rate (HR) was derived from ECG. V_o2 and O2 contents of arterial and mixed venous blood samples were determined at each period of observation. Oxygen contents of blood were determined by the Van Slyke-Neill method or with a calibrated Lex-O2-Con analyzer. Cardiac output (Q) was determined using the direct Fick principle.

The only complication was the occurrence in one patient of minor pulmonary infarction at the site of repeated inflation of the Swan-Ganz balloon catheter. In consequence, frequent observations of the wedged pulmonary arterial pressure were subsequently omitted from the procedure.

Observations were made during the fourth minute of rest while sitting upright on a stationary Monark bicycle ergometer, and during the fourth minute of each level of exercise in the upright posture, except during the highest level (third minute). Workloads were initiated with pedaling at 50 rev/min against zero resistance, and continued against increasing resistance loads measured in watts. There were usually no rest periods between the increasing workloads, except for a few minutes of rest just before the highest resistance workload. Each period of observation lasted four minutes, except for the period of highest workload, which was usually reduced to three minutes.

Observations were evaluated in relation to relative aerobic requirement, or percentage of maximal oxygen uptake (V_02max) measured for each person, to provide a physiological basis for comparison.

\[
\% \frac{V_{O2,\text{max}}}{V_{O2,\text{max}}} \times 100
\]

Thus, observed \( V_{o2} \) during submaximal exercise on the bicycle ergometer was related to highest possible \( V_{O2,\text{max}} \) attained by maximal exercise on a treadmill.* 100% \( V_{O2,\text{max}} \) - \( V_{o2} \) defines aerobic reserve for more strenuous exertion at a given submaximal workload.

Significance of (mean) differences was evaluated by Student's t-test for unpaired data.

### Results

#### Maximal Exercise on the Treadmill

Weight-adjusted \( V_{O2,\text{max}} \) of all 42 CHD patients and of 11 healthy men averaged 24.5 ± 6.1 and 35.9 ± 7.1 ml/ (kg·min), respectively (P < 0.001). Mean durations were 382 ± 136 sec versus 565 ± 136 sec (P < 0.001), while FAI values were 30.7 ± 15.3% versus 1.4 ± 18.0% for these groups (P < 0.001).

When the coronary patients were separated according to whether or not they experienced angina with exercise testing, mean duration averaged 432 ± 126 sec without angina versus 321 ± 129 sec with angina (P < 0.01). Corresponding values for FAI were 26 ± 15% and 37 ± 13% (P < 0.05). As indicated in table 2, maximal heart rate, systolic pressure and pressure-rate product, as well as changes in heart rate and changes in systolic pressure from minimal values at rest to those of maximal exercise were lowest in the angina patients, intermediate in the non-angina patients and highest in the healthy men. These observations, derived by clinical methods of monitoring ECG for heart rate and taking blood pressure by sphygmomanometry, indicated significant differences in relation to severity of coronary vascular disease as manifested by angina.

#### Submaximal Exercise on the Bicycle Ergometer

Aerobic requirements and hemodynamic respons-

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*Normally peak \( V_{o2} \) observed with exercise on a bicycle averages only 94% of peak \( V_{o2} \) observed in the same subjects during exercise on a treadmill.*
Table 2

Responses to Maximal Exercise of Multistage Treadmill Test

<table>
<thead>
<tr>
<th></th>
<th>Normals (mean ± sd)</th>
<th>Without pain</th>
<th>CHD patients (mean ± sd)</th>
<th>With pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>11</td>
<td>23</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Duration (sec)</td>
<td>565 ± 136</td>
<td>432 ± 126†</td>
<td>321 ± 124‡</td>
<td></td>
</tr>
<tr>
<td>Max HR (beats/min)</td>
<td>170 ± 12</td>
<td>158 ± 26</td>
<td>145 ± 23†</td>
<td></td>
</tr>
<tr>
<td>Max SBP (mm Hg)</td>
<td>199 ± 19</td>
<td>172 ± 35*</td>
<td>158 ± 35†</td>
<td></td>
</tr>
<tr>
<td>(\dot{V}_O_2)max (ml/min)</td>
<td>2727 ± 467</td>
<td>2063 ± 469‡</td>
<td>1608 ± 358‡</td>
<td></td>
</tr>
<tr>
<td>(\dot{V}_O_2) (ml/kg·min⁻¹)</td>
<td>35.9 ± 7.1</td>
<td>26.6 ± 6.0‡</td>
<td>21.9 ± 5.2‡</td>
<td></td>
</tr>
<tr>
<td>(\Delta H R) (beats/min) (max-rest HR)</td>
<td>100 ± 17</td>
<td>81 ± 23*</td>
<td>67 ± 23‡</td>
<td></td>
</tr>
<tr>
<td>(\Delta S B P) (mm Hg) (max-rest BP)</td>
<td>73 ± 22</td>
<td>41 ± 34†</td>
<td>33 ± 27‡</td>
<td></td>
</tr>
<tr>
<td>Max PR/100</td>
<td>337 ± 40</td>
<td>275 ± 81*</td>
<td>231 ± 71‡</td>
<td></td>
</tr>
<tr>
<td>FAI (%)</td>
<td>1 ± 18</td>
<td>26 ± 15‡</td>
<td>37 ± 13‡</td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05, in relation to normals.
†P < 0.01, in relation to normals.
‡P < 0.001, in relation to normals.

es to sitting at rest and to four levels of submaximal exercise in two groups of coronary patients and healthy men are presented in table 3 and figures 1, 2 and 3.

\(\dot{Q}\) was linearly related and directly proportional to \(\dot{V}_O_2\) (fig. 1). When coronary patients were subdivided according to presence or absence of exertional angina, the rate of change of \(\dot{Q}\) relative to \(\dot{V}_O_2\) (or slope of the regression line) was less in the angina patients (\(P < 0.03\)). More importantly, the limits of \(\dot{Q}\) and \(\dot{V}_O_2\) at 87-90% of \(\dot{V}_O_2\)max were greatly reduced (\(P < 0.001\)) in the angina patients. The component mechanisms of impaired circulatory delivery of oxygen are represented by three-dimensional diagrams of absolute values for the minimal and near-maximal aerobic requirements observed (fig. 2). Variations over all workloads studied are illustrated one variable at a time against relative aerobic requirements, or \% \(\dot{V}_O_2\)max (fig. 3). The three-dimensional diagrams suggest a reduced SV, particularly in patients who develop pain of angina with exertion, but little difference in either HR or A-V O₂ D at rest. With near-maximal exercise, both SV and HR are restricted, especially in coronary patients with pain. Minor differences in A-V O₂ D are not statistically significant. Thus, although both \(\dot{V}_O_2\) and \(\dot{Q}\) were greatly limited,
peripheral extraction was nearly as great as in either patients without pain or healthy men; indeed, this corroborated the symptomatic evidence of a close approximation to actual $V_{O_{2\text{max}}}$.

Further insights into component mechanisms of impairment are provided by examination of the relationships of these and other variables to several levels of relative aerobic requirement, or $\% V_{O_{2\text{max}}}$ (fig. 3). Now it becomes apparent that there is little difference in mean values of SV in or peripheral resistance between patients who developed exertional pain and those without pain. When aerobic requirement exceeds 60\% $V_{O_{2\text{max}}}$, there is a significant restriction in HR, together with an inadequate increment in systemic mean arterial pressure ($P_{\text{SA}}$). Pressure-rate product ($PR$) is also lower, yet the changes in ratio of systemic mean to pulmonary mean ($P_{\text{PA}}$) arterial pressure are not altered in relation to coronary disease or occurrence of chest pain. To emphasize the circumstances of these observations, the lower physical workloads in watts and lower absolute $V_{O_{2}}$ requirements at near-maximal effort for these three groups are also shown in figure 3.

**Discussion**

FAI of ambulatory cardiac patients represents a quantitative objective assessment of total cardiovascular function in relation to expected values of $V_{O_{2\text{max}}}$ in appropriate healthy peers. Thus, it contrasts in method and in frame of reference to the traditional subjective appraisal of symptoms, as recalled, in relation to "ordinary" activities of undefined severity, scaled from class I to class IV.
Table 3

Hemodynamic Responses at Rest and to Upright Exercise

<table>
<thead>
<tr>
<th></th>
<th>Normal Without pain</th>
<th>CHD Without pain</th>
<th>Normal With pain</th>
<th>Exercise 1 Without pain</th>
<th>CHD With pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of observations</td>
<td>11</td>
<td>23</td>
<td>19</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>W O₂load (watts)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14 ± 29</td>
<td>12 ± 19</td>
</tr>
<tr>
<td>V O₂ (ml/min)</td>
<td>317 ± 48</td>
<td>302 ± 49</td>
<td>296 ± 57</td>
<td>633 ± 294</td>
<td>628 ± 219</td>
</tr>
<tr>
<td>% V O₂max</td>
<td>12 ± 2</td>
<td>15 ± 4</td>
<td>18 ± 5</td>
<td>22 ± 9</td>
<td>29 ± 8</td>
</tr>
<tr>
<td>FAI (%)</td>
<td>0 ± 19</td>
<td>26 ± 15‡</td>
<td>37 ± 13‡</td>
<td>0 ± 19</td>
<td>29 ± 13‡</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>70 ± 25</td>
<td>63 ± 15</td>
<td>59 ± 18</td>
<td>83 ± 20</td>
<td>83 ± 23</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>81 ± 15</td>
<td>77 ± 12</td>
<td>80 ± 17</td>
<td>93 ± 21</td>
<td>84 ± 18</td>
</tr>
<tr>
<td>A-V O₂ D (ml/liter)</td>
<td>59 ± 10</td>
<td>64 ± 13</td>
<td>66 ± 11</td>
<td>81 ± 16</td>
<td>91 ± 15</td>
</tr>
<tr>
<td>Q (liters/min)</td>
<td>5.50 ± 1.29</td>
<td>4.87 ± 1.21</td>
<td>4.66 ± 1.60</td>
<td>7.63 ± 2.29</td>
<td>6.87 ± 1.93</td>
</tr>
<tr>
<td>Ppa (mm Hg)</td>
<td>99 ± 16</td>
<td>102 ± 13</td>
<td>104 ± 14</td>
<td>110 ± 15</td>
<td>119 ± 17</td>
</tr>
<tr>
<td>Ppa (mm Hg)</td>
<td>11 ± 2</td>
<td>12 ± 3</td>
<td>11 ± 4</td>
<td>15 ± 4</td>
<td>18 ± 4</td>
</tr>
<tr>
<td>Ppa/Ppa</td>
<td>9.11 ± 1.61</td>
<td>9.25 ± 2.23</td>
<td>10.06 ± 3.32</td>
<td>7.75 ± 1.63</td>
<td>6.93 ± 1.47</td>
</tr>
<tr>
<td>Rsa (dyne-cm-sec⁻⁴)</td>
<td>1515 ± 337</td>
<td>1789 ± 547</td>
<td>1908 ± 449*</td>
<td>1228 ± 263</td>
<td>1435 ± 366</td>
</tr>
<tr>
<td>Rpa (dyne-cm-sec⁻⁴)</td>
<td>170 ± 43</td>
<td>205 ± 90</td>
<td>201 ± 64</td>
<td>160 ± 31</td>
<td>216 ± 60†</td>
</tr>
<tr>
<td>PR/100</td>
<td>81 ± 19</td>
<td>79 ± 18</td>
<td>83 ± 22</td>
<td>104 ± 31</td>
<td>101 ± 33</td>
</tr>
</tbody>
</table>

Abbreviations: A-V O₂ = Arteriovenous oxygen difference; HR = Heart rate; Psa, Ppa = Mean systemic, pulmonary arterial pressure; PR = Pressure-rate produce; Q = Cardiac output; Rsa, Rpa = Mean systemic, pulmonary arterial resistance; SV = Stroke volume; V O₂ = Oxygen uptake.

*P < 0.05.
†P < 0.01.
‡P < 0.001.

According to the criteria of the New York Heart Association, FAI can be derived rapidly, reliably and safely by using a standardized multistage treadmill protocol of supervised maximal exercise testing and simple nomogram.

The significance of V O₂max is that it defines cardiovascular functional capacity for circulatory delivery of oxygen, since it is precisely equal to the product of Qmax and A-V O₂ Dmax. In health, V O₂max in liters/min is proportional to body weight, especially lean body mass, and varies normally with sex, age and physical activity status. When these characteristics are defined, V O₂max may be predicted from regression equations. The agreement between mean predicted and mean observed values for eight subgroups of healthy middle-aged persons is shown in figure 4. Finally, when FAI is determined, average % V O₂max expected in normal peers equals 100 minus FAI. When derived with the appropriate nomogram, either duration of exercise to obtain 0% FAI (i.e., 100% of average normal predicted V O₂max for a given age) or the equivalent age in years for the duration observed may be readily ascertained.

Earlier studies of cardiovascular components of V O₂max in cardiac patients appear to be limited to those of Blackman and associates on patients with mitral stenosis. Several observations from that study are relevant. At any level of work in the upright posture, a plateau in V O₂ occurred within 2-3 minutes. The approach to V O₂max was normal even

*For clinical purposes, an active person is one who participates in physical activities equivalent to jogging or running, long enough to develop sweating, at least once a week, regularly.
though level of $V_{O_{2max}}$ was greatly reduced, primarily because of restricted SV. Accordingly, $V_{O_{2max}}$ was considered to provide the most information for the least clinical procedure. Increments in HR, A-V O$_2$ D and blood lactate concentration were normal, as were decrements in estimated hepatic blood flow at any level of submaximal exercise, but only when evaluated in relation to percentage of maximal oxygen uptake.

Malmberg studied hemodynamic responses to upright exercise in 38 patients with coronary heart disease at various levels of submaximal exercise scaled to absolute values of aerobic requirements, regardless of the capacity of the patients tested. At given submaximal workloads, stroke volume and cardiac output were lower in the patients than in 11 healthy older men, the values in the patients who were unable to perform at 600 kpm (100 watts) were even lower. There was no correlation between hemodynamic responses to exercise and coronary arteriographic findings at rest, nor to electrocardiographic changes with exercise. Manifestations of left-ventricular failure during exercise in patients with a tolerance for less than 600 kpm/min emphasized the importance of exercise tolerance for evaluation of patients with coronary disease.

The salient findings of the present study are that SV and $Q$ were reduced, while peripheral resistance was increased at submaximal workloads, whether or not angina was experienced. The rate of change in $Q$ for an increment in $V_{O_{2}}$ and HR at workloads greater than 60% of $V_{O_{2max}}$ were also lower, making the values of $Q$ and $V_{O_{2}}$ even lower at near-maximal exercise in patients with anginal pain. Peripheral extraction of O$_2$ defined by A-V O$_2$ D, was not significantly restricted. Since patients with angina also tended to have lower systemic arterial pressure (and pressure-rate product) when aerobic requirements exceeded 60% $V_{O_{2max}}$, the pressure available for perfusion of stenotic coronary arteries is suboptimal. Thus, angina patients not only experience pain, but, more importantly, they exhibit much lower limits of $V_{O_{2}}$ and $Q$ from restrictions of both SV and HR at workloads that are only modest in absolute terms but nevertheless stressful in relative terms. These mechanisms compound the myocardial ischemia of exertion imposed by coronary vascular disease, while enhanced peripheral resistance appears to be a desirable, albeit in some instances excessive compensation. Evidence for the latter is implied in the transient and significant increase in $V_{O_{2max}}$ when coronary patients, whether they experience angina or not, are treated with nitroglycerin.

These findings have been supplemented by somewhat parallel observations of McDonough and associates who found that coronary patients when exercised to maximum on a treadmill exhibited plateaus in both $V_{O_{2}}$ and $Q$ when they had partial support of the catheterized arm long enough to make these observations. Furthermore, angina patients had lower $V_{O_{2max}}$ and $Q_{max}$, and $Q$ actually fell, while $V_{O_{2}}$ was maintained by a slightly greater A-V O$_2$ D with the last minute of exercise.
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