Eight patients with coronary heart disease and exertional angina pectoris successfully completed an 11-15 wk program of endurance exercise conditioning. Angina threshold was determined by upright bicycle ergometer exercise and by atrial pacing. The product of heart rate and arterial systolic blood pressure at the exercise angina threshold was higher after conditioning, suggesting that conditioning increased the maximum myocardial O$_2$ supply during exercise. However, when angina was induced by atrial pacing, heart rate, arterial blood pressure, coronary blood flow, and myocardial O$_2$ consumption at the angina threshold were the same before and after conditioning. Myocardial lactate extraction during atrial pacing was abnormal in the same five patients before and after conditioning. Conditioning caused no detectable changes in coronary collaterals as judged by coronary arteriograms.

The increase in exercise angina threshold appeared to be due to a functional adaptation in either myocardial O$_2$ supply or the relationship between hemodynamic work and myocardial O$_2$ consumption. The adaptation was limited to exercise, and did not occur during a different stress to myocardial O$_2$ supply, atrial pacing.
Investigation of the Physiological Basis for Increased Exercise Threshold for Angina Pectoris after Physical Conditioning

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**ABSTRACT** Eight patients with coronary heart disease and exertional angina pectoris successfully completed an 11-15 wk program of endurance exercise conditioning. Angina threshold was determined by upright bicycle ergometer exercise and by atrial pacing. The product of heart rate and arterial systolic blood pressure at the exercise angina threshold was higher after conditioning, suggesting that conditioning increased the maximum myocardial $O_2$ supply during exercise. However, when angina was induced by atrial pacing, heart rate, arterial blood pressure, coronary blood flow, and myocardial $O_2$ consumption at the angina threshold were the same before and after conditioning. Myocardial lactate extraction during atrial pacing was abnormal in the same five patients before and after conditioning. Conditioning caused no detectable changes in coronary collaterals as judged by coronary arteriograms.

The increase in exercise angina threshold appeared to be due to a functional adaptation in either myocardial $O_2$ supply or the relationship between hemodynamic work and myocardial $O_2$ consumption. The adaptation was limited to exercise, and did not occur during a different stress to myocardial $O_2$ supply, atrial pacing.

**INTRODUCTION**

In patients with exertional angina pectoris due to ischemic coronary disease, physical conditioning can increase the amount of exertion required to precipitate their angina (1-4). Physical conditioning alters the circulatory response to exercise, resulting in a lower heart rate and systolic blood pressure at any given work load (2-5). The decrease in these determinants of myocardial oxygen consumption after conditioning suggests that the increased tolerance for exertion in

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Of these nine, one patient who was exceptionally limited by angina was unable to progress satisfactorily in the prescribed exercises. Postconditioning coronary arteriography demonstrated progression of disease in the left circumflex and right coronary arteries. Since his underlying coronary disease progressed and he did not experience the same conditioning effect as the remaining eight patients, his data are excluded. Certain clinical and angiographic characteristics of the eight patients to be reported are presented in Table I. All patients were men. The mean age was 50 yr. Three patients had triple, one double, and four single-vessel coronary disease (>70% proximal narrowing). Four patients had a prior myocardial infarction and all had angiographic evidence of left ventricular dysfunction. All patients were in sinus rhythm, and no patient had signs or symptoms of uncompensated left ventricular failure.

**Conditioning program.** The patients lived at home and came to the hospital three days a week for exercise conditioning. At each conditioning session, patients performed dynamic endurance exercise, consisting of 30 min of alternate walking and jogging and 15 min of calisthenics designed to utilize large muscles and to cause a sustained increase in heart rate. Bicycle exercise was avoided, so that the specific activity used to test the effects of conditioning was not practiced. The exercise was prescribed for individual patients, starting at a low intensity and increasing progressively in an attempt to maintain each patient at a barely subanginal level of work. When angina did occur, patients were instructed to stop exercising and if necessary to use sublingual nitroglycerin. When angina subsided, the patients resumed exercise. Each conditioning session was supervised by one of the authors. An electrocardiogram (ECG) recorder and defibrillator were ready for immediate use. One patient (C. B.) developed ventricular fibrillation and was successfully defibrillated. He was hospitalized for observation, and there was no evidence of myocardial infarction.

Patients were instructed to maintain their normal level of home activity. They did not alter their dietary or smoking habits. All patients used sublingual nitroglycerin, two patients were treated with long-acting nitrates, and no patient received digitalis or beta adrenergic inhibition therapy. All medications were discontinued 48 h before testing procedures; smoking was discontinued 24 h before testing procedures. Conditioning was maintained up to the time of hospitalization for postconditioning study. The intervals between pre- and postconditioning studies ranged from 11 to 15 wk.

**Test protocols.** Left ventricular 35-mm cineangiography and selective coronary arteriography with 35-mm cine and high-resolution cut films in multiple projections were performed by the Judkins technique (10).

Exercise testing was performed on a Quinton Instruments Model 844 Uninonk bicycle ergometer, designed to provide a constant workload within the rpm range we used (Quinton Instruments, Seattle, Wash.). Before selection, patients underwent ergometer testing on two separate days. In each patient selected for study, angina occurred at the same work level on both occasions and constituted a crisp end point, appearing abruptly and within 20 s becoming so intense that the patient was unwilling to continue the same degree of exertion.

Data presented here were obtained on a subsequent day. The patients fasted and received no premedication. The ECG was monitored continuously with a manubrial-V5 lead. Brachial artery blood pressure obtained from an indwelling 15-cm P-60 polyethylene catheter was recorded at rest and during exercise with the patient sitting. Exercise started at an ergometer work load one step below the angina level determined previously. Workload increased by 100 kilopond-meters (kpm) per min every 3 min until angina occurred. Brachial artery blood pressure was recorded during the last 30 s of each work level and at the onset of angina (exercise angina threshold).

After recovery from the angina induced by exercise, patients lay supine and, via an antecubital vein, a bipolar pacing catheter was positioned in the coronary sinus midway between the ostium and left cardiac border. The coronary venous catheter was checked frequently to verify that its position remained stationary. In five patients, a Gensini catheter was positioned in the left ventricle from a percutaneous femoral artery approach. Supine resting observations consisted of brachial artery and left ventricular blood pressures, paired arterial and coronary venous blood sam-

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**Table I Clinical and Angiography Data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Angina duration</th>
<th>Prior MI</th>
<th>Coronary disease (&gt;70% obstruction)</th>
<th>LV dysfunction</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LAD</td>
<td>LCCA</td>
</tr>
<tr>
<td>P. E.</td>
<td>56</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>J. B.</td>
<td>51</td>
<td>½</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>I. W.</td>
<td>57</td>
<td>½</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>B. R.</td>
<td>35</td>
<td>½</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>J. S.</td>
<td>61</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>P. C.</td>
<td>39</td>
<td>½</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>M. F.</td>
<td>48</td>
<td>½</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>C. B.</td>
<td>53</td>
<td>½</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Ant, anterior wall; Gen, general; Inf, inferior wall; LAD, left anterior descending artery; LCCA, left circumflex artery; LV, left ventricle; MI, myocardial infarction; RCA, right coronary artery.

---

1 Abbreviations used in this paper: CV, coronary venous blood; ECG, electrocardiogram; RFP, rate pressure product; TP, triple product; TTI, time tension index.
<table>
<thead>
<tr>
<th>Patient</th>
<th>Cond.</th>
<th>Work</th>
<th>Dur.</th>
<th>HR</th>
<th>BPs</th>
<th>BPd</th>
<th>LVedp</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>kpm/min</td>
<td>min</td>
<td>min/min</td>
<td>mm Hg</td>
</tr>
<tr>
<td>P. E.</td>
<td>Pre 200</td>
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<td>88</td>
<td>122</td>
<td>76</td>
<td>119</td>
<td>107</td>
</tr>
<tr>
<td></td>
<td>Post 200</td>
<td>3.0</td>
<td>80</td>
<td>137</td>
<td>68</td>
<td>109</td>
<td>111</td>
</tr>
<tr>
<td>J. B.</td>
<td>Pre 200</td>
<td>2.5</td>
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<td>101</td>
<td>69</td>
<td>108</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>Post 300</td>
<td>5.8</td>
<td>56</td>
<td>105</td>
<td>70</td>
<td>117</td>
<td>140</td>
</tr>
<tr>
<td>I. W.</td>
<td>Pre 200</td>
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<td>89</td>
<td>59</td>
<td>102</td>
<td>145</td>
</tr>
<tr>
<td></td>
<td>Post 200</td>
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<td>66</td>
<td>91</td>
<td>60</td>
<td>111</td>
<td>136</td>
</tr>
<tr>
<td>B. R.</td>
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<td>67</td>
<td>113</td>
<td>76</td>
<td>144</td>
<td>128</td>
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<tr>
<td></td>
<td>Post 500</td>
<td>9.5</td>
<td>61</td>
<td>130</td>
<td>65</td>
<td>150</td>
<td>122</td>
</tr>
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<td>J. S.</td>
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<td>76</td>
<td>115</td>
<td>80</td>
<td>138</td>
<td>176</td>
</tr>
<tr>
<td></td>
<td>Post 400</td>
<td>7.7</td>
<td>72</td>
<td>125</td>
<td>72</td>
<td>143</td>
<td>171</td>
</tr>
<tr>
<td>P. C.</td>
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<td>3.9</td>
<td>78</td>
<td>121</td>
<td>85</td>
<td>120</td>
<td>113</td>
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<td>75</td>
<td>117</td>
<td>76</td>
<td>118</td>
<td>115</td>
</tr>
<tr>
<td>M. F.</td>
<td>Pre 400</td>
<td>3.8</td>
<td>65</td>
<td>135</td>
<td>68</td>
<td>120</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td>Post 500</td>
<td>7.0</td>
<td>63</td>
<td>135</td>
<td>71</td>
<td>122</td>
<td>119</td>
</tr>
<tr>
<td>C. B.</td>
<td>Pre 800</td>
<td>7.0</td>
<td>61</td>
<td>165</td>
<td>61</td>
<td>147</td>
<td>143</td>
</tr>
<tr>
<td></td>
<td>Post 800*</td>
<td>9.0*</td>
<td>55</td>
<td>152*</td>
<td>62</td>
<td>165*</td>
<td>123</td>
</tr>
<tr>
<td>Mean</td>
<td>Pre 371</td>
<td>6.5</td>
<td>66</td>
<td>120</td>
<td>68</td>
<td>124</td>
<td>130</td>
</tr>
<tr>
<td></td>
<td>Post 371</td>
<td>6.5</td>
<td>66</td>
<td>120</td>
<td>68</td>
<td>124</td>
<td>130</td>
</tr>
<tr>
<td>SEM</td>
<td>Pre 31</td>
<td>0.5</td>
<td>3</td>
<td>6</td>
<td>3</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Post 56</td>
<td>1.1</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

* Angina not induced by exercise (maximum value attained).

BPd, brachial artery diastolic blood pressure; BPs, brachial artery systolic peak blood pressure; Ex. Ang., exercise angina threshold; HR, heart rate; LVedp, left ventricular end diastolic pressure; Pace Ang., pacing angina threshold; Post, postconditioning; Pre, preconditioning; Sup., supine; Up., sitting upright.

Means and P values: for resting data, n = 8; for exercise and pacing data, n = 7 (C. B. was excluded because angina was not induced postconditioning).

Tension time index (TTI) was calculated from brachial artery mean systolic pressure times heart rate times systolic ejection period per beat (12). We have emphasized RPP data because they seem to bear the closest relationship to myocardial O2 consumption during upright exercise in man (13).

Blood O2 concentration was calculated from the Po2 and pH (Radiometer Co., Copenhagen) and hemoglobin concentration (spectrophotometric), assuming a normal O2 dissociation curve (Shappell et al., have shown that conditioning does not change O2 affinity of blood (14)). Blood lactate was determined by a modification of the method of Barker and Summerson (15). Myocardial lactate extraction (a-cv/a) less than 0.09, which is 2 SD beyond the mean value of 16 normal patients studied in our laboratory (16), was considered abnormal. Coronary blood flow was determined in three patients by the Na2O desaturation method (17) and in the other five patients by the xenon method (18, 19). We injected 100 μCi xenon-133 in 10 ml saline into the left ventricular chamber and determined the myocardial clearance rate from coronary venous blood samples obtained via the coronary sinus catheter through a stopcock manifold, collecting five 15-s samples beginning 60 s after the injection. In each patient, we used the same coronary blood flow technique before and after conditioning.

Basis for Increased Exercise Angina Threshold after Conditioning 765
Table III
Systemic Hemodynamics at the Same Submaximal Work Level before and after Conditioning

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cond.</th>
<th>HR</th>
<th>BP</th>
<th>RPP</th>
</tr>
</thead>
<tbody>
<tr>
<td>B. R.</td>
<td>Pre</td>
<td>106</td>
<td>142</td>
<td>151</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>102</td>
<td>131</td>
<td>134</td>
</tr>
<tr>
<td>P. C.</td>
<td>Pre</td>
<td>114</td>
<td>134</td>
<td>153</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>103</td>
<td>136</td>
<td>140</td>
</tr>
<tr>
<td>M. F.</td>
<td>Pre</td>
<td>132</td>
<td>175</td>
<td>231</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>121</td>
<td>190</td>
<td>231</td>
</tr>
<tr>
<td>C. B.</td>
<td>Pre</td>
<td>111</td>
<td>165</td>
<td>183</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>97</td>
<td>172</td>
<td>167</td>
</tr>
</tbody>
</table>

Abbreviations are as in previous tables.

Left ventricular myocardial oxygen consumption was calculated as the product of coronary blood flow and (a-cv)O₂ difference.

Left ventricular cineangiograms were filmed in the right anterior oblique projection at 60 frames/s while 30–35 ml Renografin 76 (E. R. Squibb & Sons, Div. of Olin Mathison Corp., New York) was injected in 2.5 s. Left ventricular volume was calculated by the area-length method of Dodge, Ballew, Sandler, and Lord (20), as modified by Greene, Carlisle, Grant, and Bunnett (21), for single-plane cineangiography. The first beat after a ventricular premature contraction was not used.

Statistics. Differences between the pre- and postconditioning data were evaluated by a paired *t* test.

RESULTS

Pre- and postconditioning systemic hemodynamic data are presented in Tables II, III, and IV and in Fig. 1. Resting heart rate in the upright sitting position was lower after conditioning (*P* < 0.02). Data at the same submaximal work level before and after conditioning were obtained in four patients (Table III). Heart rate and RPP at the same level of work were lower in these patients after conditioning.

The exercise angina threshold, as determined by bicycle ergometer testing, was higher after conditioning in all patients. In the patient (C.B.) with the highest exercise angina threshold before conditioning, angina could not be provoked by ergometer testing after conditioning. The increase in exercise angina threshold in the other seven patients was significant, as judged by the work level reached (*P* < 0.05) or the duration of exercise (*P* < 0.005). Not only was the work increased, but the brachial artery systolic blood pressure and RPP at the onset of angina (exercise angina threshold) were higher after conditioning (Fig. 1). The angina threshold as determined by atrial pacing, however, was not increased by conditioning. Heart rate, brachial artery and left ventricular end diastolic blood pressures, and RPP

![Figure 1](image-url)

Figure 1 The effect of conditioning on systemic hemodynamic factors indirectly related to myocardial O₂ consumption. The heart rate (HR), brachial artery systolic blood pressure (BP), and their product (RPP) at the exercise angina threshold were higher after conditioning. Conditioning exerted no influence, however, on the values for these same hemodynamic factors at the pacing angina threshold.

Table IV
Indirect Indices of Myocardial O₂ Consumption

<table>
<thead>
<tr>
<th>Index</th>
<th>Cond.</th>
<th>Rest</th>
<th>Ex.</th>
<th>Rest</th>
<th>Pace</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPP</td>
<td>Pre</td>
<td>94±6</td>
<td>175±16</td>
<td>99±7</td>
<td>179±15</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>85±6</td>
<td>206±19</td>
<td>96±7</td>
<td>181±15</td>
</tr>
<tr>
<td></td>
<td><em>P</em> value</td>
<td>&lt;0.02</td>
<td>&lt;0.005</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>TP</td>
<td>Pre</td>
<td>252±24</td>
<td>445±34</td>
<td>283±17</td>
<td>405±33</td>
</tr>
<tr>
<td></td>
<td>Post</td>
<td>221±15</td>
<td>487±33</td>
<td>285±20</td>
<td>394±26</td>
</tr>
<tr>
<td></td>
<td><em>P</em> value</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>TTI</td>
<td>Pre</td>
<td>227±30</td>
<td>396±29</td>
<td>257±14</td>
<td>365±26</td>
</tr>
<tr>
<td></td>
<td>Post</td>
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<td>258±18</td>
<td>361±22</td>
</tr>
<tr>
<td></td>
<td><em>P</em> value</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Numbers represent means±SEM. For resting data, *n* = 8; for exercise and pacing data, *n* = 7 (C. B. excluded). Abbreviations as in previous tables.
at the pacing angina threshold were virtually the same before and after conditioning (Table II and Fig. 1). Various indirect indices used to estimate changes in myocardial O₂ consumption are presented in Table IV. Before conditioning, RPP, TP, and TTI at exercise and pacing angina thresholds were not significantly different \( (P > 0.05) \). With each of these indices, the mean value after conditioning was higher for exercise angina threshold and unchanged for pacing angina threshold.

The effects of exercise conditioning on more direct measurements of myocardial O₂ supply are presented in Table V and Fig. 2. Mean values for coronary blood flow and myocardial O₂ consumption at rest were slightly less after conditioning, but the differences were not statistically significant. Atrial pacing increased coronary blood flow and myocardial O₂ consumption in all patients; however, the values reached at the subangina pacing level were not significantly different before and after conditioning. There was no significant change in coronary (a-v)O₂ after conditioning, in contrast to the widened systemic (a-v)O₂ reported by other investigators \( (5, 22) \).

Before conditioning, five of the eight patients had an abnormally low myocardial lactate \( (L) \) extraction \( (L[a-cv/a]<0.09) \) at their pacing angina threshold. After conditioning, lactate extraction at the pacing angina threshold was again abnormal in each of the same five patients and again normal in the other three. Pre- and postconditioning mean values for myocardial lactate extraction were not significantly different either at rest or during pacing.

There were no significant differences between pre- and postconditioning mean values for left ventricular end diastolic volumes and ejection fraction at rest (Table VI).

We could detect no changes in the status of the basic coronary artery disease nor in the degree of coronary collateral circulation as judged by cine and large-cut film coronary arteriograms performed before and after the exercise conditioning in these eight patients.

### Table V

**Myocardial O₂ Supply**

<table>
<thead>
<tr>
<th>Patient</th>
<th>C(a-cv)/O₂</th>
<th>PaO₂</th>
<th>PcvO₂</th>
<th>CBF</th>
<th>MyOVO₂</th>
<th>La</th>
<th>L(a-cv)/a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ml/100 ml</td>
<td>mmHg</td>
<td>ml/100 g·min</td>
<td>ml/100 ml</td>
<td>mmHg</td>
<td>ml/100 g·min</td>
<td>mmol/liter</td>
</tr>
<tr>
<td>Pre</td>
<td>15.0</td>
<td>83</td>
<td>139</td>
<td>11.3</td>
<td>14.0</td>
<td>0.51</td>
<td>0.46</td>
</tr>
<tr>
<td>Post</td>
<td>15.4</td>
<td>82</td>
<td>85</td>
<td>7.7</td>
<td>9.7</td>
<td>0.40</td>
<td>0.41</td>
</tr>
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<td>79</td>
<td>85</td>
<td>9.8</td>
<td>12.5</td>
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<td>0.43</td>
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<td>72</td>
<td>8.4</td>
<td>11.4</td>
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<td>0.38</td>
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<td>B. R.</td>
<td>15.3</td>
<td>85</td>
<td>54</td>
<td>6.8</td>
<td>11.1</td>
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<td>11.3</td>
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<td>12.4</td>
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<td>72</td>
<td>7.6</td>
<td>11.3</td>
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<td>0.26</td>
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<td>SEM</td>
<td>0.7</td>
<td>0.5</td>
<td>0.3</td>
<td>0.6</td>
<td>0.5</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>P Value</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Angina not induced by pacing (maximum value attained).

CBF, coronary blood flow; cv, coronary venous blood; L, lactate; Myo VO₂, myocardial O₂ consumption; Sub Ang. Pace, subangina pacing level.

Means and P values: for resting data, \( n = 8 \); for pacing data, \( n = 7 \) (C. B. excluded).

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**Basis for Increased Exercise Angina Threshold after Conditioning** 767
DISCUSSION

The increase in exercise angina threshold, the decrease in resting heart rate, and the decrease in heart rate at the same submaximal work are evidence that our patients did experience a conditioning effect from the exercise program. A major objective of this study was to determine whether the increase in exercise angina threshold that occurred was due to increased myocardial O2 supply. In approaching this question, we have assumed that exertional angina pectoris is related to myocardial hypoxia and occurs when the maximum coronary blood flow has been reached.

In regard to the first assumption, the presence of myocardial hypoxia was judged by abnormal extraction of lactate by the myocardium. To provoke myocardial hypoxia, we increased the myocardial O2 requirement by atrial pacing and determined lactate extraction when angina occurred. Lactate extraction at the pacing angina threshold was abnormal in five of the eight patients before exercise conditioning. The failure to identify chemical evidence of myocardial hypoxia from samples of coronary venous blood in the other three patients presumabaly is due to the focal nature of myocardial hypoxia (14, 23). Samples of coronary venous blood were withdrawn, as near as technically possible, from the same location in the coronary venous system before and after conditioning. Precisely the same patients exhibited similar chemical evidence of myocardial hypoxia when tested at a comparable pacing-induced heart rate stress before and after conditioning. Also, patients exhibiting normal lactate extraction before conditioning remained normal after conditioning. We interpret these data as our strongest evidence that exercise conditioning did not change myocardial O2 supply, at least during angina induced by atrial pacing.

The second assumption implies that coronary blood flow at the angina threshold is the maximum coronary blood flow attainable by the patient. If conditioning augmented myocardial O2 supply, one might expect the increase in O2 supply to be reflected by an increase in maximum coronary blood flow (or, more specifically, myocardial O2 consumption). The procedures necessary to determine coronary blood flow require more time, and we believed that it would be safer and technically more satisfactory to utilize some level of stress below the angina threshold by a small and standard amount. We selected a heart rate 10 beat/min below the atrial pacing

![Figure 2](image-url)  
**Figure 2** The effect of conditioning on the submaximum myocardial O2 supply. Atrial pacing at 10 beat/min below the heart rate level which provoked angina (subangina pacing level) increased the coronary blood flow (CBF) and myocardial O2 consumption (Myo \( \dot{V}_{O2} \)), whereas (a-cv)O2 remained constant. Values for (a-cv)O2, coronary blood flow, and myocardial O2 consumption at the subangina pacing level were not higher after conditioning.

### Table VI

**Left Ventricular Volume Data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cond.</th>
<th>HR</th>
<th>EDV</th>
<th>ESV</th>
<th>EF</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Pre/Post</td>
<td>min^-1</td>
<td>m/l</td>
<td>m/l</td>
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<tr>
<td>P. E.</td>
<td>Pre/Post</td>
<td>88</td>
<td>88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J. B.</td>
<td>Pre/Post</td>
<td>82</td>
<td>87</td>
<td></td>
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<tr>
<td>I. W.</td>
<td>Pre/Post</td>
<td>63</td>
<td>66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. R.</td>
<td>Pre/Post</td>
<td>139</td>
<td>113</td>
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<tr>
<td>J. S.</td>
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<td>72</td>
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<tr>
<td>P. C.</td>
<td>Pre/Post</td>
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<td>68</td>
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<tr>
<td>C. B.</td>
<td>Pre/Post</td>
<td>106</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>Pre/Post</td>
<td>94</td>
<td>82</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEM</td>
<td>Pre/Post</td>
<td>9</td>
<td>6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume.
rate that induced angina and defined this as the sub-
angina pacing level. Although this is not a measure
of the maximum coronary blood flow, it seemed to us
that a change in the maximum coronary blood flow
would produce and could be identified by a comparable
change in the subangina coronary blood flow. Mean
values for coronary blood flow (and myocardial O\textsubscript{2}
consumption) at the subangina pacing levels before and
after conditioning were not different. A major limita-
tion of the blood flow data on heterogeneity of myo-
cardial ischemia is recognized. Coronary blood flow
values determined by either the N\textsubscript{2}O or xenon clearance
method reflect mainly the relatively normally perfused
myocardium and are less influenced by the ischemic
regions (23, 24). Our coronary blood flow data by
themselves, therefore, certainly might be incapable of
detecting increased blood flow in local ischemic regions
of the myocardium after conditioning. The unaltered
pacing angina threshold and myocardial lactate extrac-
tion, however, do not suggest increased blood flow to a
local ischemic region.

Up to this point we have discussed myocardial O\textsubscript{2}
supply during atrial pacing, when myocardial O\textsubscript{2}
consumption could be measured and angina pectoris
substantiated by independent chemical evidence of myo-
cardial hypoxia. With exercise testing, we relied upon
angina as the end point signaling the onset of myocardial
hypoxia and RPP as an indirect indicator of myocardial
O\textsubscript{2} consumption. Detry and Bruce (9) found that con-
ditioning altered the relationship between angina and
ST segment depression as manifestations of myocardial
hypoxia during exercise. Their patients experienced
angina at a higher RPP after conditioning but developed
ST segment depression at the same RPP as before con-
ditioning, which raises some doubt about the physi-
ologic significance of a higher threshold for angina. We
obtained satisfactory exercise ECG recordings in six
of our patients. One patient showed no ST segment
depression. In the other five patients, angina was ac-
companied by ST segment depression in both the pre-
and postconditioning exercise tests. Our ECG data un-
fortunately are not adequate for a more detailed com-
parison with the RPP data.

The higher RPP at the exercise angina threshold in
our patients after conditioning agrees with results re-
ported previously by other investigators (4, 9). How-
ever, our data also indicate an unexpected difference
between exercise and pacing tachycardia. Indirect in-
dices of myocardial O\textsubscript{2} consumption at the angina
threshold after conditioning were higher for exercise
but not for pacing (Table IV). The systemic hemo-
dynamic, lactate extraction, and coronary blood flow
data during pacing are internally consistent in demon-
strating no increase in myocardial O\textsubscript{2} supply. Consid-
ered together with the systemic hemodynamic data dur-
ing exercise, the results suggest that exercise condition-
ing exerted some effect that pertained specifically to ex-
ercise and did not carry over to a different stress, pacing-
induced tachycardia. This effect could be explained by
either of two alternative hypotheses: (a) conditioning
increased maximum myocardial O\textsubscript{2} supply only during
exercise, or (b) conditioning changed the relationship
(only during exercise) between the systemic hemo-
dynamic factors believed to be indirect indices of myo-
cardial O\textsubscript{2} consumption on the one hand, and the actual
O\textsubscript{2} consumption, on the other. Since we were unable to
obtain the critical measurements of myocardial O\textsubscript{2}
supply during exercise needed to distinguish between
these hypotheses, their assessment must be indirect.

The first hypothesis implies a coronary vasomotor
response to increased myocardial O\textsubscript{2} consumption that
occurred during exercise but not during atrial pacing
and, therefore, would require a modification of the
widely accepted relationship between local myocardial
metabolic needs and coronary vascular resistance. For
the second hypothesis, there are several possible ex-
planations for increased systemic hemodynamic factors
without a corresponding increase in myocardial O\textsubscript{2}
consumption, which include supplementary anaerobic energy
supply, decreased left ventricular volume, and decreased
myocardial contractile state. Although exercise condi-
tioning in rats increases the glycogen stores (25–27),
lactic dehydrogenase activity (28), and mechanical
performance of their hearts under hypoxic conditions
(29), an increase in their capacity for myocardial
anaerobic metabolism has not been demonstrated (26,29).
Moreover, the lactate data in our patients showed
no effect of conditioning on myocardial lactate produc-
tion during atrial pacing. Left ventricular volume, as
judged by angiography, was not different before and
after conditioning in our patients, which is consistent
with results reported by Frick and Katila (2). Admit-
tedly, these ventricular volume observations were made
in the resting state, not during exercise. Among the
possible explanations for a decrease in myocardial O\textsubscript{2}
consumption relative to concurrent RPP that would
pertain to exercise but not atrial pacing, a change in
myocardial contractile state is perhaps the most likely.
In the first place, exercise involves adrenergic stimula-
tion of the heart to a much greater degree than pacing.
Furthermore, the decrease in catecholamine concentra-
tion in hearts of conditioned rats (30) and the attenu-
ated effect of autonomic blockade on exercise tachy-
cardia in conditioned humans (31) suggest that adrener-
gic stimulation of the heart during exercise may be less
after conditioning.

The increase in exercise capacity after exercise condi-
tioning in patients who are limited by angina pectoris
appears to be due to a functional adaptation in either the delivery or utilization of O2 in the myocardium, rather than to a static alteration in the coronary circulation. Coronary arteries as judged by arteriography in the resting state were not detectably altered. The functional adaptation did not appear to operate during a different stress, atrial pacing. Since the adaptation seems to be restricted to exercise, the measurements needed to identify it with certainty may have to be made while the patient is exercising.

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REFERENCES