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### Research Article

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The increase in exercise angina threshold appeared to be due to a functional adaptation in either myocardial  $Q$  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.

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# 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

patients with a limited myocardial  $O_2$  supply might be due to a lower myocardial oxygen requirement at any given level of exertion.

Increased myocardial  $O_2$  supply is another possible explanation for the higher exercise threshold for angina. There is evidence that exercise conditioning in rats increases their coronary vascularity (6), maximum coronary blood flow, and myocardial  $O_2$  consumption (7), and that exercise in dogs with coronary stenosis promotes coronary collateral development (8). Furthermore, it has been reported that after conditioning, patients with coronary heart disease can reach higher values of heart rate and systolic blood pressure before angina develops during exercise (4, 9). If one accepts heart rate and systolic blood pressure as indirect indices of myocardial  $O_2$  consumption, the higher values attained suggest a higher maximum myocardial  $O_2$  supply.

Our objective is to investigate the physiological basis for the increased exercise threshold for angina pectoris, and especially to define more clearly the effect of physical conditioning on myocardial  $O_2$  supply. We evaluated myocardial  $O_2$  supply from (a) indirect indices of myocardial  $O_2$  consumption; (b) measurements of coronary blood flow, myocardial  $O_2$  consumption, and myocardial lactate extraction, and (c) coronary arteriography.

## METHODS

**Patient description.** Subjects were selected from patients undergoing evaluation for angina pectoris. Criteria were: (a) history of disabling but stable angina pectoris, (b) angina pectoris induced by bicycle ergometer testing, (c) significant coronary artery disease as documented by coronary arteriography, (d) willingness to participate in the conditioning program and test procedures, and (e) no other disability incompatible with exercise conditioning. We selected 12 patients. Three could not continue the conditioning exercises due to the emergence of latent orthopedic problems. Nine patients completed the conditioning program and the pre- and postconditioning test procedures.

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TABLE I  
Clinical and Angiography Data

| Patient | Age | Angina duration | Prior MI | Coronary disease (>70% obstruction) |      |     | LV dysfunction |     |     |
|---------|-----|-----------------|----------|-------------------------------------|------|-----|----------------|-----|-----|
|         |     |                 |          | LAD                                 | LCCA | RCA | Ant            | Inf | Gen |
|         | yr  | yr              |          |                                     |      |     |                |     |     |
| P. E.   | 56  | 5               |          | +                                   | +    | +   |                | +   |     |
| J. B.   | 51  | $\frac{1}{2}$   |          | +                                   |      |     | +              |     |     |
| I. W.   | 57  | $\frac{1}{2}$   |          |                                     | +    |     |                |     | +   |
| B. R.   | 35  | $\frac{1}{2}$   | +        | +                                   | +    | +   | +              |     |     |
| J. S.   | 61  | 4               |          | +                                   | +    | +   |                | +   |     |
| P. C.   | 39  | $\frac{3}{4}$   | +        | +                                   |      |     | +              |     |     |
| M. F.   | 48  | $\frac{3}{4}$   | +        | +                                   |      | +   | +              | +   |     |
| C. B.   | 53  | $\frac{1}{2}$   | +        |                                     |      | +   |                | +   |     |

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.

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)<sup>1</sup> 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.

<sup>1</sup>Abbreviations used in this paper: cv, coronary venous blood; ECG, electrocardiogram; RPP, rate pressure product; TP, triple product; TTI, time tension index.

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 Uniwork 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-

TABLE II  
Systemic Hemodynamics

| Patient | Cond. | Work           | Dur.       | HR       |                         |           |           | BP <sub>s</sub> |              |           |           | BP <sub>d</sub> |              |           |           | LV <sub>edp</sub> |              |
|---------|-------|----------------|------------|----------|-------------------------|-----------|-----------|-----------------|--------------|-----------|-----------|-----------------|--------------|-----------|-----------|-------------------|--------------|
|         |       |                |            | Rest Up. | Ex. Ang.                | Rest Sup. | Pace Ang. | Rest Up.        | Ex. Ang.     | Rest Sup. | Pace Ang. | Rest Up.        | Ex. Ang.     | Rest Sup. | Pace Ang. | Rest Sup.         | Pace Ang.    |
|         |       | <i>kpm/min</i> | <i>min</i> |          | <i>min<sup>-1</sup></i> |           |           |                 | <i>mm Hg</i> |           |           |                 | <i>mm Hg</i> |           |           |                   | <i>mm Hg</i> |
| P. E.   | Pre   | 200            | 1.8        | 88       | 122                     | 76        | 119       | 107             | 119          | 121       | 134       | 70              | 71           | 76        | 93        | —                 | —            |
|         | Post  | 200            | 3.0        | 80       | 137                     | 68        | 109       | 111             | 149          | 132       | 140       | 72              | 84           | 79        | 95        | —                 | —            |
| J. B.   | Pre   | 200            | 2.5        | 65       | 103                     | 69        | 108       | 144             | 154          | 146       | 154       | 80              | 87           | 80        | 94        | 10                | 5            |
|         | Post  | 300            | 5.8        | 56       | 105                     | 70        | 117       | 140             | 188          | 156       | 158       | 78              | 93           | 84        | 104       | 16                | 11           |
| I. W.   | Pre   | 200            | 1.8        | 63       | 89                      | 59        | 102       | 145             | 154          | 139       | 140       | 76              | 76           | 70        | 88        | 11                | 6            |
|         | Post  | 200            | 3.0        | 66       | 91                      | 60        | 111       | 136             | 154          | 141       | 139       | 72              | 74           | 72        | 92        | 16                | 4            |
| B. R.   | Pre   | 300            | 4.0        | 67       | 113                     | 76        | 144       | 128             | 142          | 124       | 126       | 80              | 84           | 74        | 84        | 21                | 9            |
|         | Post  | 500            | 9.5        | 61       | 130                     | 65        | 150       | 122             | 141          | 120       | 113       | 76              | 76           | 69        | 77        | 15                | 9            |
| J. S.   | Pre   | 300            | 5.3        | 76       | 115                     | 80        | 138       | 176             | 182          | 170       | 176       | 88              | 90           | 90        | 111       | —                 | —            |
|         | Post  | 400            | 7.7        | 72       | 125                     | 72        | 143       | 171             | 200          | 186       | 178       | 88              | 99           | 95        | 117       | —                 | —            |
| P. C.   | Pre   | 300            | 3.9        | 78       | 121                     | 85        | 120       | 113             | 140          | 118       | 122       | 66              | 78           | 68        | 79        | 16                | 12           |
|         | Post  | 500            | 9.5        | 75       | 117                     | 76        | 118       | 115             | 159          | 123       | 135       | 69              | 87           | 72        | 88        | 19                | 18           |
| M. F.   | Pre   | 400            | 3.8        | 65       | 136                     | 68        | 120       | 116             | 179          | 128       | 177       | 64              | 94           | 76        | 111       | —                 | —            |
|         | Post  | 500            | 7.0        | 63       | 135                     | 71        | 122       | 119             | 206          | 141       | 158       | 63              | 93           | 77        | 101       | —                 | —            |
| C. B.   | Pre   | 800            | 7.0        | 61       | 165                     | 61        | 147       | 143             | 222          | 138       | 168       | 81              | 100          | 79        | 120       | 17                | 9            |
|         | Post  | 800*           | 9.0*       | 55       | 152*                    | 62        | 165*      | 123             | 212*         | 122       | 130*      | 71              | 100*         | 67        | 98*       | 9                 | 4*           |
| Mean    | Pre   | 271            | 3.3        | 70       | 114                     | 72        | 122       | 134             | 153          | 136       | 147       | 76              | 83           | 77        | 94        | 15                | 8            |
|         | Post  | 371            | 6.5        | 66       | 120                     | 68        | 124       | 130             | 171          | 140       | 146       | 74              | 87           | 77        | 96        | 15                | 11           |
| SEM     | Pre   | 31             | 0.5        | 3        | 6                       | 3         | 6         | 9               | 9            | 6         | 9         | 3               | 3            | 3         | 5         | 3                 | 2            |
|         | Post  | 56             | 1.1        | 3        | 7                       | 2         | 6         | 7               | 11           | 8         | 8         | 3               | 4            | 3         | 5         | 2                 | 3            |
| P value |       | <0.02          | <0.005     | <0.02    | NS                      | NS        | NS        | NS              | <0.02        | NS        | NS        | NS              | NS           | NS        | NS        | NS                | NS           |

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

BP<sub>a</sub>, brachial artery diastolic blood pressure; BP<sub>s</sub>, brachial artery systolic peak blood pressure; Ex. Ang., exercise angina threshold; HR, heart rate; LV<sub>edp</sub>, 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).

ples for O<sub>2</sub>, pH, and lactate analyses, and coronary blood flow. Atrial pacing began at a rate 10 beat/min above the resting heart rate and increased by 10 beat/min every 3 min until chest pain typical for the patient's exertional angina pectoris was definitely established (pacing angina threshold). After a recovery period of at least 15 min, pacing was restarted at a rate 10 beat/min below the pacing angina threshold just established (subangina pacing level). Paired arterial and coronary venous blood samples for O<sub>2</sub> and pH analyses were collected and coronary blood flow was determined at the subangina pacing level. Paired arterial and coronary venous blood samples for lactate analyses were drawn at the pacing angina threshold.

**Laboratory techniques.** Pressures were recorded on a photographic Electronics for Medicine Recorder (Electronics for Medicine, Inc., White Plains, N. Y.) with P23Gb Statham transducers (Statham Instruments, Inc., Oxnard, Calif.). Pressure transducer zero level was at the sternal angle for the upright exercise studies. Systolic ejection period was measured on the brachial artery tracing recorded at a paper speed of 100 mm/s. Rate pressure product (RPP) was calculated from brachial artery systolic peak pressure times heart rate (11). Triple product (TP) was calculated from brachial artery systolic peak pressure times heart rate times systolic ejection period per beat (4).

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 O<sub>2</sub> consumption during upright exercise in man (13).

Blood O<sub>2</sub> concentration was calculated from the PO<sub>2</sub> and pH (Radiometer Co., Copenhagen) and hemoglobin concentration (spectrophotometric), assuming a normal O<sub>2</sub> dissociation curve (Shappell et al., have shown that conditioning does not change O<sub>2</sub> 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 N<sub>2</sub>O desaturation method (17) and in the other five patients by the xenon method (18, 19). We injected 100  $\mu$ Ci 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.

TABLE III  
Systemic Hemodynamics at the Same Submaximal Work Level before and after Conditioning

| Patient | Cond. | HR  | BP <sub>s</sub> | RPP |
|---------|-------|-----|-----------------|-----|
| B. R.   | Pre   | 106 | 142             | 151 |
|         | Post  | 102 | 131             | 134 |
| P. C.   | Pre   | 114 | 134             | 153 |
|         | Post  | 103 | 136             | 140 |
| M. F.   | Pre   | 132 | 175             | 231 |
|         | Post  | 121 | 190             | 231 |
| C. B.   | Pre   | 111 | 165             | 183 |
|         | Post  | 97  | 172             | 167 |

Abbreviations are as in previous tables.

Left ventricular myocardial oxygen consumption was calculated as the product of coronary blood flow and (a-cv)O<sub>2</sub> 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 Mathieson 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 Bunnell (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

TABLE IV  
Indirect Indices of Myocardial O<sub>2</sub> Consumption

| Index                    | Cond. | Rest Up.     | Ex. Ang.     | Rest Sup.    | Pace Ang.    |
|--------------------------|-------|--------------|--------------|--------------|--------------|
| RPP ( $\times 10^{-2}$ ) | Pre   | 94 $\pm$ 6   | 175 $\pm$ 16 | 99 $\pm$ 7   | 179 $\pm$ 15 |
|                          | Post  | 85 $\pm$ 6   | 206 $\pm$ 19 | 96 $\pm$ 7   | 181 $\pm$ 15 |
| <i>P</i> value           |       | <0.02        | <0.005       | NS           | NS           |
| TP ( $\times 10^{-1}$ )  | Pre   | 252 $\pm$ 24 | 445 $\pm$ 34 | 283 $\pm$ 17 | 405 $\pm$ 33 |
|                          | Post  | 221 $\pm$ 15 | 487 $\pm$ 33 | 285 $\pm$ 20 | 394 $\pm$ 26 |
| <i>P</i> value           |       | <0.05        | <0.01        | NS           | NS           |
| TTI ( $\times 10^{-1}$ ) | Pre   | 227 $\pm$ 20 | 396 $\pm$ 29 | 257 $\pm$ 14 | 365 $\pm$ 26 |
|                          | Post  | 202 $\pm$ 12 | 431 $\pm$ 29 | 258 $\pm$ 18 | 361 $\pm$ 22 |
| <i>P</i> value           |       | NS           | <0.05        | NS           | NS           |

Numbers represent means  $\pm$  SEM. For resting data,  $n = 8$ ; for exercise and pacing data,  $n = 7$  (C. B. excluded). Abbreviations as in previous tables.

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

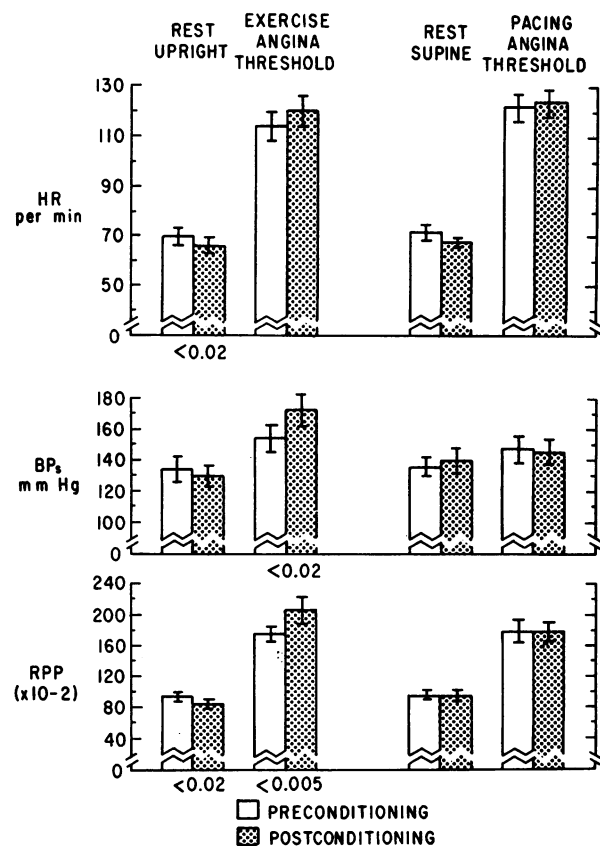


FIGURE 1 The effect of conditioning on systemic hemodynamic factors indirectly related to myocardial O<sub>2</sub> consumption. The heart rate (HR), brachial artery systolic blood pressure (BP<sub>s</sub>), and their product (RPP) at the exercise angina threshold were higher after conditioning. Conditioning exerted no influence, however, on the values for these same hemodynamic factors at the pacing angina threshold.

TABLE V  
Myocardial O<sub>2</sub> Supply

| Patient | Cond. | CaO <sub>2</sub> |               | C(a-cv)O <sub>2</sub> |               | PaO <sub>2</sub> |               | Pcvo <sub>2</sub> |               | CBF          |               | Myo $\dot{V}O_2$ |               | La         |           | L(a-cv/a) |           |
|---------|-------|------------------|---------------|-----------------------|---------------|------------------|---------------|-------------------|---------------|--------------|---------------|------------------|---------------|------------|-----------|-----------|-----------|
|         |       | Rest             | Sub ang. pace | Rest                  | Sub ang. pace | Rest             | Sub ang. pace | Rest              | Sub ang. pace | Rest         | Sub ang. pace | Rest             | Sub ang. pace | Rest       | Pace ang. | Rest      | Pace ang. |
|         |       | ml/100 ml        |               | ml/100 ml             |               | mm Hg            |               | mm Hg             |               | ml/100 g·min |               | ml/100 g·min     |               | mmol/liter |           |           |           |
| P. E.   | Pre   | 14.9             | 15.0          | 10.4                  | 10.1          | 80               | 83            | 18.9              | 20.0          | 109          | 139           | 11.3             | 14.0          | 0.51       | 0.46      | 0.06      | 0.17      |
|         | Post  | 14.7             | 15.4          | 9.3                   | 10.2          | 82               | 88            | 22.1              | 21.1          | 83           | 95            | 7.7              | 9.7           | 0.40       | 0.41      | 0.35      | 0.10      |
| J. B.   | Pre   | 18.1             | 18.3          | 11.5                  | 11.8          | 74               | 77            | 22.1              | 22.0          | 85           | 106           | 9.8              | 12.5          | 0.44       | 0.43      | 0.23      | -0.09     |
|         | Post  | 17.7             | 17.7          | 11.5                  | 11.9          | 79               | 79            | 22.0              | 21.1          | 82           | 90            | 9.4              | 10.7          | 0.41       | 0.42      | 0.27      | 0.02      |
| I. W.   | Pre   | 18.0             | 18.0          | 12.0                  | 11.4          | 88               | 84            | 21.1              | 22.2          | 72           | 88            | 8.6              | 10.0          | 0.44       | 0.46      | 0.32      | 0.30      |
|         | Post  | 19.3             | 19.4          | 12.4                  | 11.6          | 78               | 81            | 21.7              | 23.1          | 68           | 98            | 8.4              | 11.4          | 0.38       | 0.38      | 0.26      | 0.32      |
| B. R.   | Pre   | 20.2             | 20.2          | 12.6                  | 12.8          | 85               | 91            | 21.6              | 21.7          | 54           | 87            | 6.8              | 11.1          | 0.44       | 0.39      | 0.30      | -0.07     |
|         | Post  | 20.1             | 20.3          | 12.8                  | 13.5          | 83               | 85            | 21.9              | 21.2          | 54           | 99            | 6.9              | 13.4          | 0.41       | 0.42      | 0.15      | -0.07     |
| J. S.   | Pre   | 18.1             | 18.3          | 12.2                  | 11.6          | 73               | 80            | 20.2              | 21.5          | 71           | 98            | 8.7              | 11.4          | 0.41       | 0.45      | 0.27      | 0.02      |
|         | Post  | 19.1             | 19.6          | 11.8                  | 11.7          | 71               | 81            | 22.0              | 23.0          | 65           | 105           | 7.7              | 12.3          | 0.41       | 0.42      | 0.27      | 0.03      |
| P. C.   | Pre   | 18.3             | 18.3          | 11.9                  | 11.9          | 79               | 80            | 21.8              | 22.0          | 99           | 108           | 11.8             | 12.9          | 0.38       | 0.41      | 0.18      | 0.07      |
|         | Post  | 19.3             | 18.9          | 11.4                  | 11.6          | 76               | 81            | 23.6              | 23.1          | 69           | 105           | 7.9              | 12.2          | 0.36       | 0.32      | 0.22      | -0.16     |
| M. F.   | Pre   | 15.4             | 15.3          | 9.5                   | 9.9           | 71               | 71            | 22.9              | 22.3          | 80           | 129           | 7.6              | 12.8          | 0.35       | 0.35      | 0.26      | -0.03     |
|         | Post  | 16.3             | 16.4          | 9.7                   | 9.6           | 74               | 73            | 22.9              | 23.5          | 96           | 120           | 9.3              | 11.5          | 0.50       | 0.46      | 0.12      | -0.15     |
| C. B.   | Pre   | 16.9             | 17.6          | 10.5                  | 9.8           | 86               | 103           | 22.9              | 25.2          | 70           | 127           | 7.4              | 12.4          | 0.47       | 0.46      | 0.21      | 0.22      |
|         | Post  | 17.2             | 17.5*         | 11.8                  | 10.5*         | 82               | 84*           | 20.0              | 23.1*         | 63           | 116*          | 7.4              | 12.2*         | 0.68       | 0.48      | 0.32      | 0.10      |
| Mean    | Pre   | 17.5             | 17.6          | 11.3                  | 11.4          | 80               | 81            | 21.4              | 21.7          | 80           | 108           | 9.0              | 12.1          | 0.43       | 0.43      | 0.23      | 0.07      |
|         | Post  | 18.0             | 18.2          | 11.3                  | 11.4          | 78               | 81            | 22.0              | 22.3          | 73           | 102           | 8.1              | 11.6          | 0.44       | 0.41      | 0.25      | 0.02      |
| SEM     | Pre   | 0.6              | 0.7           | 0.4                   | 0.4           | 2                | 2             | 0.5               | 0.3           | 6            | 7             | 0.6              | 0.5           | 0.02       | 0.01      | 0.03      | 0.05      |
|         | Post  | 0.7              | 0.7           | 0.4                   | 0.5           | 2                | 2             | 0.4               | 0.4           | 5            | 4             | 0.3              | 0.5           | 0.04       | 0.02      | 0.03      | 0.05      |
| P Value |       | NS               | NS            | NS                    | NS            | NS               | NS            | NS                | NS            | NS           | NS            | NS               | NS            | NS         | NS        | NS        | NS        |

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

CBF, coronary blood flow; cv, coronary venous blood; L, lactate; Myo  $\dot{V}O_2$ , myocardial O<sub>2</sub> consumption; Sub Ang. Pace, subangina pacing level. Means and P values: for resting data, *n* = 8; for pacing data, *n* = 7 (C. B. excluded).

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 O<sub>2</sub> 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 O<sub>2</sub> supply are presented in Table V and Fig. 2. Mean values for coronary blood flow and myocardial O<sub>2</sub> consumption at rest were slightly less after conditioning, but the differences were not statistically significant. Atrial pacing increased coronary blood flow and myocardial O<sub>2</sub> 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)O<sub>2</sub> after conditioning, in contrast to the

widened systemic (a-v)O<sub>2</sub> 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.

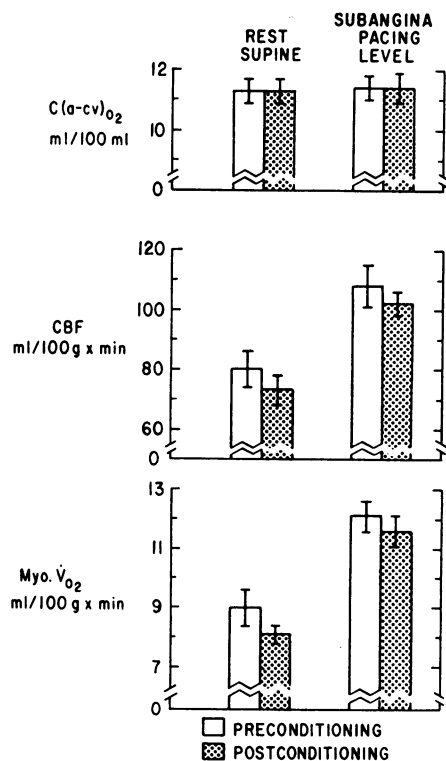


FIGURE 2 The effect of conditioning on the submaximum myocardial  $O_2$  supply. Atrial pacing at 10 beat/min below the heart rate level which provoked angina (subangina pacing level) increased the coronary blood flow (CBF) and myocardial  $O_2$  consumption ( $Myo \cdot \dot{V}O_2$ ), whereas  $(a-cv)O_2$  remained constant. Values for  $(a-cv)O_2$ , coronary blood flow, and myocardial  $O_2$  consumption at the subangina pacing level were not higher after conditioning.

## 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  $O_2$  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  $O_2$  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 pre-

sumably 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  $O_2$  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  $O_2$  supply, one might expect the increase in  $O_2$  supply to be reflected by an increase in maximum coronary blood flow (or, more specifically, myocardial  $O_2$  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

TABLE VI  
Left Ventricular Volume Data

| Patient | Cond. | HR         | EDV      | ESV      | EF   |
|---------|-------|------------|----------|----------|------|
|         |       | $min^{-1}$ | $ml/m^2$ | $ml/m^2$ |      |
| P. E.   | Pre   | 88         | —        | —        | 0.49 |
|         | Post  | 88         | —        | —        | 0.56 |
| J. B.   | Pre   | 82         | 109      | 24       | 0.78 |
|         | Post  | 87         | 73       | 22       | 0.70 |
| I. W.   | Pre   | 63         | 140      | 56       | 0.60 |
|         | Post  | 66         | 148      | 66       | 0.55 |
| B. R.   | Pre   | 139        | 151      | 73       | 0.52 |
|         | Post  | 113        | 136      | 67       | 0.51 |
| J. S.   | Pre   | 88         | 123      | 65       | 0.48 |
|         | Post  | 72         | 99       | 34       | 0.66 |
| P. C.   | Pre   | 92         | 106      | 42       | 0.61 |
|         | Post  | 68         | 103      | 47       | 0.55 |
| C. B.   | Pre   | 106        | 72       | 36       | 0.51 |
|         | Post  | 77         | 104      | 41       | 0.61 |
| Mean    | Pre   | 94         | 117      | 49       | 0.57 |
|         | Post  | 82         | 111      | 46       | 0.59 |
| SEM     | Pre   | 9          | 11       | 8        | 0.04 |
|         | Post  | 6          | 11       | 7        | 0.03 |
| P Value |       | NS         | NS       | NS       | NS   |

EDV, end diastolic volume; EF, ejection fraction; ESV, end systolic volume.

rate that induced angina and defined this as the subangina 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  $O_2$  consumption) at the subangina pacing levels before and after conditioning were not different. A major limitation of the blood flow data on heterogeneity of myocardial ischemia is recognized. Coronary blood flow values determined by either the  $N_2O$  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 extraction, however, do not suggest increased blood flow to a local ischemic region.

Up to this point we have discussed myocardial  $O_2$  supply during atrial pacing, when myocardial  $O_2$  consumption could be measured and angina pectoris substantiated by independent chemical evidence of myocardial 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  $O_2$  consumption. Detry and Bruce (9) found that conditioning 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 conditioning, which raises some doubt about the physiologic 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 accompanied by ST segment depression in both the pre- and postconditioning exercise tests. Our ECG data unfortunately are not adequate for a more detailed comparison with the RPP data.

The higher RPP at the exercise angina threshold in our patients after conditioning agrees with results reported previously by other investigators (4, 9). However, our data also indicate an unexpected difference between exercise and pacing tachycardia. Indirect indices of myocardial  $O_2$  consumption at the angina threshold after conditioning were higher for exercise but not for pacing (Table IV). The systemic hemodynamic, lactate extraction, and coronary blood flow data during pacing are internally consistent in demonstrating no increase in myocardial  $O_2$  supply. Consid-

ered together with the systemic hemodynamic data during exercise, the results suggest that exercise conditioning exerted some effect that pertained specifically to exercise 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  $O_2$  supply only during exercise, or (b) conditioning changed the relationship (only during exercise) between the systemic hemodynamic factors believed to be indirect indices of myocardial  $O_2$  consumption on the one hand, and the actual  $O_2$  consumption, on the other. Since we were unable to obtain the critical measurements of myocardial  $O_2$  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  $O_2$  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 explanations for increased systemic hemodynamic factors without a corresponding increase in myocardial  $O_2$  consumption, which include supplementary anaerobic energy supply, decreased left ventricular volume, and decreased myocardial contractile state. Although exercise conditioning 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 production 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). Admittedly, these ventricular volume observations were made in the resting state, not during exercise. Among the possible explanations for a decrease in myocardial  $O_2$  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 stimulation of the heart to a much greater degree than pacing. Furthermore, the decrease in catecholamine concentration in hearts of conditioned rats (30) and the attenuated effect of autonomic blockade on exercise tachycardia in conditioned humans (31) suggest that adrenergic stimulation of the heart during exercise may be less after conditioning.

The increase in exercise capacity after exercise conditioning in patients who are limited by angina pectoris



appears to be due to a functional adaptation in either the delivery or utilization of O<sub>2</sub> 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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