Reproduction of Maximal Exercise Performance in Patients with Angina Pectoris Despite Ouabain Treatment

By Manfred Niederberger, M.D., Robert A. Bruce, M.D., Richard Frederick, M.S., Fusako Kusumi, M.S., and Arthur Marriott, B.S.

SUMMARY

Eight patients with a diagnosis of atherosclerotic heart disease and a history of typical angina pectoris, uncomplicated by cardiac dilatation or heart failure, were studied by means of standardized, symptom-limited treadmill exercise test. Repeatability of such testing was determined during two control tests 1–1.5 hours apart. From two to six days later, the same patients performed two treadmill tests after pulmonary and brachial arterial catheterization. The study design allowed evaluation of the effects of 0.005 mg/kg of ouabain at rest—both supine and standing—and during submaximal and maximal exercise.

Measurements were made of oxygen uptake, arterial-mixed venous oxygen difference, heart rate, systemic arterial pressures and pulmonary arterial mean pressure. The ratio of mean systemic to mean pulmonary arterial pressure relative to cardiac output indicated that acute left ventricular dysfunction limited aerobic work. Treatment with ouabain did not significantly change performance or capacity and angina was not alleviated.

Additional Indexing Words:

Ischemic (coronary) heart disease
Arterial-mixed venous oxygen difference
Maximal oxygen uptake

ATTAINTMENT OF THE LEVEL of maximal exercise by patients with angina pectoris is often limited by chest pain, dyspnea, and fatigue, together with greatly reduced endurance levels, lower maximal oxygen uptake, maximal heart rate, and pressure-rate product.1,2 Recent hemodynamic observations revealed restricted cardiac output (Q), stroke volume (SV), and even arterial—mixed venous oxygen difference (A-VO2 D) in severely impaired patients.3 These findings suggest acute left ventricular dysfunction secondary to rather severe myocardial ischemia resulting from coronary vascular disease which limited supply of oxygenated blood. Whether cardiac glycosides could improve function is controversial in view of the fact that they might exert a positive inotropic effect, further compromising an ischemic left ventricle. Some reports suggest improved left ventricular performance, whereas others show alleviation of angina or greater exercise capacity, or both, in some patients.4–8 Although cardiac glycosides increase contractility of the left ventricle and improve function of dilated and failing heart, they do not increase myocardial efficiency in the nonfailing heart.9 Administration of digoxin fails to cause increase in either the duration of sustained isometric exercise or the maximal dynamic exercise in healthy men regardless of whether adequate time for recovery from prior stress is permitted.10

This study was designed to observe possible acute effects of ouabain therapy in patients with angina pectoris uncomplicated by congestive heart failure, both at rest, whether supine or standing, and during exercise, whether submaximal or maximal. In addition to usual hemodynamic criteria at maximal performance, the ratio of mean systemic to mean pulmonary arterial pressure was plotted against cardiac output and was used to identify any other

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309
changes in limits of cardiac function with therapy in relation to increasing aerobic stress of exercise. Any independent effects of these stresses on reproducibility of hemodynamic responses were also appraised.

Subjects and Method
Among eight patients (seven men and one woman) selected for study, mean age was 56 (range 42–68) years, average height 177 (173–183) cm, and average weight 74 (61–89) kg. The diagnosis of atherosclerotic heart disease was established in all by history of typical angina pectoris with exertional stresses and manifestations in the electrocardiogram (ECC) of postexertional myocardial ischemia (horizontal or downsloping ST segment depression of more than 0.1 mV). Two patients (B.O. and W.I.) also had healed myocardial infarctions, while two others (T.H. and L.A.) had angiographic documentation of at least 70% narrowing of one or more of the three major coronary arteries. Heart sizes of all eight were within normal limits. None had clinical manifestations of heart failure or findings suggestive of heart disease from other causes, e.g., hypertension. None was anemic or had evidence of pulmonary disease by chest X-ray and pulmonary-function screening tests. None had diabetes mellitus or was limited in exercise performance by intermittent claudication or skeletal-muscular disease. None of the patients had received any medication for at least two weeks preceding the study, with the exception of nitroglycerin which was discontinued on the days of the study.

All patients participated voluntarily, giving their informed consent after appropriate explanations. Seven had been participants in the rehabilitation program of the Cardio-Pulmonary Research Institute (CAPRI), where they exercised for at least one-half hour three times a week under medical supervision, but only three had been active for the past three months. The other four had been inactive; accordingly it was unrealistic to expect any significant physiologic changes from training.

The study design is shown in figure 1. At least two hours after a light breakfast and after a physical examination, a standardized multistage treadmill test (Test 1) was performed; this was repeated after 75–90 min of bed rest (Test 2) to ascertain the repeatability of exercise responses. Seven patients had had previous treadmill tests. In all tests, they were advised to go to the limits of exercise capacity before symptoms (pain, fatigue, dyspnea) developed. They indicated the onset of chest pain and signaled when the test should be terminated. No test was stopped prematurely by the investigating physicians. Immediately after completion of the test, the patient was asked to give the primary reason(s) for stopping. Blood pressure was determined with a clinical sphygmomanometer. Methods for determination of oxygen uptake (\(V_{O_2}\)) and heart rate in Tests 1 and 2 were the same as described below for Tests 3 and 4. Functional aerobic impairment (FAI) was derived from duration of Test 1 by use of nomograms.

Hemodynamic studies were conducted two to six days after Tests 1 and 2. After a light breakfast and another physical examination, a Swan-Ganz catheter (French size 7) was placed under pressure-monitoring through a left antecubital vein into a pulmonary artery. A Teflon catheter was inserted into the left brachial artery. Pressures were recorded by the same Statham

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**Figure 1**
Schematic diagram of test protocol that was strictly observed in all patients, with the exception of one subject (L.A.) who had only one control treadmill (TM) test (Test 1) rather than two. Circles indicate periods of three minutes, in which \(V_{O_2}\), arterial-mixed venous oxygen difference (A-VO\(_2\) D), brachial arterial pressures, pulmonary arterial mean pressures, and HR were measured simultaneously. During exercise, the same measurements were recorded over one-minute periods at the end of each stage of the TM test and in the last 2-3 consecutive minutes of the test.
pressure transducers (P23Gb for systemic and P23V for pulmonary arterial pressures) in all tests and mean pressures were derived continuously by electrical averaging. With the patient supine, the zero pressure reference was adjusted 10 cm above the mattress. In the upright position, zero pressure reference was located at the fourth anterior intercostal space, and it was moved with the patient as the gradient of the treadmill was increased. The transthoracic bipolar ECG lead was continuously displayed on an oscilloscope and recorded on magnetic tape, along with both pulsatile and mean blood pressures. Heart rate was obtained from the ECG, recorded at a paper speed of 25 mm/sec. Cardiac output (Q) was obtained by taking blood samples during collection of expired air for measurement of Vo2 (direct Fick method). Mixed venous and arterial blood was sampled from the pulmonary and brachial arteries, respectively, and oxygen content was measured with a calibrated Lex-O2-Con analyzer.12 The total amount of blood withdrawn did not exceed 140 ml. Vo2 was determined from expired air, sampled over three-minute periods at rest and over one-minute periods during exercise, breathing into evacuated neoprene bags. After two supine measurements, the subjects walked to the treadmill, where measurements were obtained while standing at rest, in the last minute of each three-minute stage, and consecutively each minute during the last 2-3 minutes of exercise. A special support was used to keep the patients’ catheterized arms steady during exercise. For some patients, both tests were started with "5%" stage (1.7 miles/hr, 5% gradient); otherwise all tests followed the standardized procedure11 Time 0 for calculation the total duration of each test was always adjusted to the beginning of stage I (1.7 miles/hr, 10% gradient).

The durations of standing at rest before the measurements were the same and the timing of all other measurements was exactly the same in both tests. Supine measurements after Test 3 were taken as shown in figure 1. Ouabain (0.005 mg/kg body weight) was injected 45 minutes after termination of Test 3, over a two-minute period, through the Swan-Ganz catheter that was then flushed with saline. This dosage of ouabain was equivalent to the "full digitalization" dosage by single intravenous injection of 0.25 to 0.50 mg of ouabain as listed by Goodman and Gilman.13

After three more supine measurements (fig. 1), Test 4 was performed 45 minutes after treatment with ouabain, observing exactly the same protocol as in Test 3. The patients were again advised to go to their limits as in Test 3. After completion of Test 4, the catheters were removed, and the subjects were kept under medical supervision for at least two hours and were then discharged from the hospital.

Statistical analysis of data used Student's paired or unpaired t-tests, as indicated in the table and figures. P values greater than 0.05 were considered not significant (NS).

Results

Comparison of the results of Tests 1 and 2 (fig. 2) shows no significant differences in blood pressure or heart rate (HR) at submaximal exercise loads and satisfactory reproducibility of VO2max and HRmax. Six of seven subjects exercised insignificantly longer in Test 2. One subject (L.A.) performed only one control test (fig. 3). Four patients who experienced chest pain in all tests were designated group A, while four others who did not experience angina in any tests formed group B. Longer duration of Tests 3 and 4 than of Tests 1 and 2 is attributed to partial support from the device used to steady the catheterized arm. In Test 4, three subjects exercised slightly longer than in Test 3 (fig. 3); they stopped primarily because of shortness of breath in both tests 3 and 4, although one also had angina chest pain. The other five subjects were symptomatically limited by chest pain or fatigue.

Results of the hemodynamic studies involving tests 3 and 4 are shown in detail, along with the statistical analysis, in table 1. They can be summarized as follows: 30-40 minutes after completion of a symptom-limited treadmill test, resting HR and pressure-rate product (PR) were higher than before, despite lower mean systemic arterial pressure (FA). Q and VO2 were unchanged, and as a result, stroke volume (SV) was smaller. Treatment with ouabain (0.005 mg/kg) did not significantly change any variable at rest or during exercise, including the estimated mean value of left ventricular end-diastolic pressure (Pd) from observed pulmonary arterial mean pressure and stroke volume14 of approximately 20 mm Hg at maximal exercise. All subjects had exertional horizontal or downsloping ST segment depression of more than 0.1 mV. The numbers of premature beats were similar in both tests 3 and 4. Responses to maximal exercise of four patients in group A are equivalent to results for all eight patients and show no changes after treatment (table 1).

Discussion

In general, the initial reproducibility of hemodynamic measurements was satisfactory, yet there was prolonged minor, but significant, relative tachycardia with no clear explanation15 at rest after maximal exercise testing. Previous studies in normals showed the importance of dissipation of endogenous heat load when dynamic exercise was repeated within ten minutes,10 but the time interval allowed in this study design should have been ample to exclude any residual thermal effect. When retested after 1-1.5 hours, duration of such exercise tended to be longer in six of seven patients, and peak VO2 slightly
Table 1

Hemodynamic Measurements and Statistical Analysis

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<td>665</td>
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All values are rounded.

*P < 0.001.
†P < 0.05.

Abbreviations: m = mean; sn = standard deviation; A–VO₂ D = arterio–venous oxygen difference; DBP = diastolic blood pressure; FM = final minute; FM-I = final minute minus 1; HR = heart rate; Pₚₚₚ = mean pulmonary arterial pressure; Pₛₚₚₚ = mean systemic arterial pressure; PP = pulmonary pressure; PR = pressure-rate product; Q = cardiac output; SBP = systolic blood pressure; SRI = systemic resistance; SV = stroke volume; VO₂ = oxygen uptake; % VO₂ max = percent maximal oxygen uptake.
Results (mean ± sd) of Tests 1 and 2 for seven subjects. One patient (L.A.) was not included because she did not perform Test 2. At stage 1 (third minute), only measurements of HR, SBF, and DBP were taken in all cases, while in the final minute of exercise (maximum), only HR and \( V_{O_2} \) were measured at all. None of the measurements showed significant differences between Test 1 and Test 2 (Student's paired t-test). Abbreviations: \( V_{O_2} \) = oxygen uptake; SBF = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; SPR = systolic pressure-rate product; PP = pulmonary pressure.

higher, but these minor improvements were not statistically significant.

Treatment with ouabain produced only insignificant changes in all variables studied, including an 8% increase of average SV in supine patients. The lack of significance in this change was a function of both the magnitude of variance and the relatively small number of patients studied. The average heart rate while standing at rest increased 20 beats/min (\( P < 0.05 \)); but since the cardiac output was virtually unchanged, stroke volume fell. Whether this was coincidental could not beascertained. No effects on calculated systemic resistance were observed at rest or during exercise. At submaximal exercise, the patients showed negligible increments in \( Q \) when treated with ouabain, yet peak \( Q \) did not increase.

Several criteria were available in this study to assess the limits of cardiovascular functions; they included \( V_{O_2} \), A-VO\(_2\) D, HR, \( Q \), SV, systemic arterial pressure (P\(_{SA}\)), mean pulmonary arterial pressure (P\(_{PA}\)), PR, and ratio of P\(_{SA}\)/P\(_{PA}\). Since \( Q \) did not appreciably increase, or even decrease in the last two minutes of the test, while the ratio between P\(_{SA}\) and P\(_{PA}\) fell, acute dysfunction of the left ventricle as a primary limitation to aerobic work was suggested (fig. 4). After ouabain treatment, all measurements, including PR, were essentially unchanged when this occurred.

Although the same cardiovascular limits were attained before and after treatment, during strenuous exercise after ouabain, this occurred earlier in five out of eight patients. Thus, while a tendency toward longer duration and higher peak \( V_{O_2} \) was noted without treatment, these trends were reversed after treatment with ouabain.

These findings support the observations of Smith et al.,\(^8\) who found no improvement in the treadmill
Figure 3

Duration of treadmill tests in seconds. (L.A. was not included when durations of Test 1 and Test 2 were compared by Student's paired t-test.) Functional aerobic impairment (FAI) was derived for each subject from duration of Test 1 by use of nomograms, taking age, sex, and physical activity status into account. Inasmuch as FAI normally averages $0 \pm 11\%$, five of the eight patients had values which were more than two standard deviations beyond the mean.

Figure 4

Ratio of mean systemic to mean pulmonary arterial pressures, ($P_{SA}/P_{PA}$), related to cardiac output ($Q$). FM indicates final minute, FM - 1, final minus one, and FM - 4, final minus four minutes. Note increments in $Q$ with slowly decreasing pressure ratio at submaximal exercise and virtually identical $Q$ in the last two minutes (FM - 1, FM) of maximal exercise, while the pressure ratio dropped. Arrows indicate possible changes with study design (NS) which occurred only with submaximal exercise. Values are mean values of eight subjects.

Exercise performance after treatment with lanatoside C of patients with angina pectoris in the absence of heart failure. Similarly, in normal men without heart disease, treatment with digoxin did not improve exercise capacity.

Partial disagreement of our results with the findings of others who reported beneficial effects of treatment with cardiac glycosides in some patients with angina$^4$, $^7$, $^8$ may be attributed to differences in selection of patients and in type of exercise test and study protocol used.

In conclusion, the findings presented in this study of selected patients with angina pectoris document the reproducibility of hemodynamic responses to submaximal and maximal treadmill exercise. Furthermore, they indicate that in the absence of cardiac enlargement or manifestations of heart failure, treatment with a cardiac glycoside neither prevented nor delayed acute coronary insufficiency nor improved performance of the ischemic left ventricle during such exercise, whether angina pectoris occurred or not.

Our observations do not, of course, preclude the possibility of benefit of treatment with cardiac...
glycosides in other patients with angina pectoris that is complicated by cardiac dilatation and congestive heart failure.

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