Studies on Digitalis

VI. Reduction of the Oxygen Debt after Exercise with Digoxin in Cardiac Patients without Heart Failure

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It is undisputed that the administration of digitalis to patients with many forms of congestive heart failure results in an improvement in both the clinical state and in the abnormal circulatory dynamics that are characteristic of heart failure. The effects of digitalis in subjects without heart failure are less well defined. Although some glycosides augment the contractile force of non-failing hearts of patients with heart disease, and increase the rate of intraventricular pressure development in intact normal subjects, these drugs have not been shown to elevate the cardiac output at rest and during exercise in normal subjects or in patients with heart disease without failure. When administered acutely to patients with "latent" heart failure, an improvement of circulatory dynamics occurs in some individuals, but not in all. In view of the conflicting interpretations of these observations, the role of digitalis in the treatment of patients with heart disease but without heart failure is not clear. Accordingly, the present investigation was designed to assess the effects of digitalis on the response of the cardiovascular system to the stress of muscular exercise in patients with heart disease and cardiac enlargement without clinical evidence of congestive heart failure.

One of the fundamental functions of the cardiovascular system is delivery of oxygen for metabolism in tissues at rest and during activity. The inability of the cardiovascular system to perform this function adequately results in the accumulation of excess lactate, and the development of an abnormally high oxygen debt during exertion. The development of an oxygen debt is characteristic of congestive failure. It was therefore thought that accurate measurement of the oxygen debt after exercise might provide an appropriate means of evaluating the effects of cardiac glycosides on the adequacy of circulatory function.

Description of Patients

The three patients chosen as the subjects for this study all had inactive rheumatic valvular disease, cardiomegaly, and a history of cardiac decompensation some months or years previously, but had none of the clinical signs of congestive heart failure at the time of study. These three patients were selected because they were capable of performing light physical activities without cardiac symptoms in the absence of digitalis therapy. They did not complain of orthopnea or paroxysmal nocturnal dyspnea. Detailed and repeated physical examinations during the course of the investigation failed to disclose rales at the lung bases at rest or during exercise; the patients were free from edema, had normal levels of systemic venous pressure, and did not have clinical evidence of hepatic enlargement.

C.A. (no. 02-57-64) is a 54-year-old man with rheumatic mitral regurgitation and stenosis. Easy fatigability, exertional dyspnea, and peripheral edema had developed 5 years prior to study and he had been maintained on digitalis, a diuretic regimen, and a low-sodium diet for several years. Physical examination indicated the presence of rheumatic mitral regurgitation and stenosis. The electrocardiogram showed atrial fibrillation, left axis deviation, and left bundle-branch block. Chest x-ray and fluoroscopy revealed enlargement of the left atrium and left ventricle. The patient was maintained on a diet containing 1 Gm. of sodium daily and he received 1 Gm. of chlorothiazide daily throughout the study. He was studied on 10 occasions on nine separate days during three periods (fig. 1). During the first period he was maintained on a daily dose of 0.25 mg. of digoxin. The glycoside was replaced by a placebo during the second period. He was then redigitalized with 4.75 mg.

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of digoxin given over a 6-day period and during the third period of the study he was maintained on 0.50 mg. of digoxin daily.

P.F. (no. 02-28-79) is a 38-year-old man in whom a heart murmur was detected in 1949 and who developed exertional dyspnea and paroxysmal nocturnal dyspnea in 1957. On physical examination he was considered to have rheumatic mitral regurgitation. He had slight cardiac enlargement with left ventricular predominance on roentgenographic examination. The electrocardiogram showed normal sinus rhythm and left ventricular hypertrophy and strain. However, combined right and left heart catheterizations in February 1959 demonstrated that intracardiac pressures and the cardiac index were within normal limits. He was maintained on a diet containing 800 mg. of sodium and he received 50 mg. of hydrochlorothiazide daily throughout the study during which the oxygen debt was measured. Two determinations of oxygen debt were made while he received 0.50 mg. of digoxin, and three studies were carried out after this drug had been discontinued and a placebo had been substituted. In addition to his usual activities the patient walked 3 miles daily without symptoms throughout the period of study.

S.M. (no. 03-54-72), a 19-year-old girl known to have rheumatic heart disease since 1949, developed signs and symptoms of congestive heart failure for the first time during a recurrence of acute rheumatic fever in 1957. She was maintained on digitalis and a low-sodium diet and had no symptoms except for occasional palpitations during strenuous exertion. On examination she was considered to have the murmurs of mitral regurgitation and stenosis and aortic regurgitation. The electrocardiogram showed sinus rhythm and first-degree atrioventricular block, left atrial enlargement, and left ventricular hypertrophy. She received a diet containing 500 mg. of sodium daily throughout the study. The postexercise oxygen debt was determined on five occasions, while she received no medication. She was then digitalized with 2.50 mg. of digoxin during a 48-hour period, received 0.50 mg. on the third day and 0.25 mg. as daily maintenance thereafter. Eight studies were carried out while she was receiving this dose (fig. 2).

*Figure 1*

Body weight and venous pressure of patient C.A. during the period of study. The vertical arrows indicate the days on which the exercise studies were carried out. The patient had been maintained on digoxin (0.25 mg. daily) for 3 years prior to the first study period.
The exercise studies were carried out on a motor-driven treadmill at speeds of 2.1 to 2.5 miles per hour and at grades of 0 to 7.5 per cent. All patients had undergone extensive training on the treadmill several times weekly for 4 to 6 weeks prior to the study. Thus, they were thoroughly familiar with the procedure so that alterations in their performance during the period of investigation could not be attributed to further training during the study. The specific conditions under which each patient was studied are presented in detail in table 1. The exercise was carried out in a Metabolic Chamber, which is an air-conditioned room maintained at constant temperature and humidity. The open-circuit method of indirect calorimetry was employed for measurement of oxygen consumption (\( \Delta V \)). The technic and instrumentation employed have been described in detail elsewhere (fig. 3). Briefly, the subject's head is enclosed by a light vinyl plastic hood suspended from the ceiling. A relatively large volume of fresh air enters the hood through an imperfect seal about the shoulders. Air is continuously drawn from the hood through appropriate tubing at a constant rate approximating 10 times the subject's respiratory minute volume during

*Figure 2*

Body weight of patient S.M. during the period of study. The vertical arrows indicate the specific days on which the exercise studies were carried out. On several of these days more than one oxygen debt after exercise was measured (table 1).
Table 1

Summary of Oxygen Debts after Exercise

<table>
<thead>
<tr>
<th>Pt.</th>
<th>B.S.A. M.²</th>
<th>Digoxin</th>
<th>Date</th>
<th>M.P.H.</th>
<th>Grade</th>
<th>Dur.</th>
<th>Pre-exercise excess VO₂ ml/min.</th>
<th>Total excess VO₂ ml.</th>
<th>O₂ debt ml</th>
<th>Total excess VO₂ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.A.</td>
<td>+</td>
<td>4/26/60</td>
<td>2.1</td>
<td>0%</td>
<td>10</td>
<td>182</td>
<td>3543</td>
<td>496</td>
<td>468</td>
<td>20</td>
</tr>
<tr>
<td>C.S. #1</td>
<td>-</td>
<td>5/6/60</td>
<td>2.1</td>
<td>0</td>
<td>10</td>
<td>240</td>
<td>3882</td>
<td>427</td>
<td>336</td>
<td>11</td>
</tr>
<tr>
<td>C.S. #2</td>
<td>-</td>
<td>11/22/61</td>
<td>2.5</td>
<td>5%</td>
<td>4'1&quot;</td>
<td>195</td>
<td>1941</td>
<td>893</td>
<td>46</td>
<td>40</td>
</tr>
<tr>
<td>C.S. #2</td>
<td>-</td>
<td>12/19/61</td>
<td>2.5</td>
<td>5%</td>
<td>4'1&quot;</td>
<td>200</td>
<td>1804</td>
<td>433</td>
<td>24</td>
<td>7</td>
</tr>
</tbody>
</table>

*Body weight was 112.64 Kg on 2/1, 110.27 Kg on 2/8, and 109.27 Kg on 2/10.
C.S. #1 weighed 71.4 Kg, C.S. #2 weighed 45.4 Kg.
Pt., patient; B.S.A., body surface area in M.²; C.S., control subject; +, study done while patient was receiving digoxin; -, no digoxin; VO₂, oxygen consumption; patient carried external weight totaling 14.72 Kg during the study designated with * *

exercise. The total flow rate of air is continuously monitored and aliquots of the stream are directed to a modified Beckman F₃ paramagnetic oxygen analyzer, located outside the chamber. The analyzer functions with an operational sensitivity of about ±0.02 per cent oxygen on the scale range used. It is calibrated and standardized with gases of known oxygen concentrations. The output of the gas analyzer was recorded on a Leeds-Northrup recorder at intervals of 3 seconds. The response of the system to a known square wave change of gas concentration in the hood was determined and utilized in the calculation of the oxygen debt following exercise (fig. 4). The total excess VO₂ resulting from exercise was calculated as the sum of the excess oxygen above control levels consumed during the actual exercise period and the oxygen debt (fig. 4).

All subjects were studied in the postabsorptive state and were weighed every morning after voiding. A minimum period of 20 minutes with the patient sitting on a chair placed on the treadmill. 

Circulation, Volume XXVII, March 1962
in the Metabolic Chamber was allowed for stabilization prior to the measurement of \( \text{Vo}_2 \) before exercise, which was also made with the patient in the sitting position. When a stable \( \text{Vo}_2 \) before exercise was achieved, the subject was asked to stand and start walking. The transition from sitting to walking or vice versa took 15 seconds or less. Immediately following the exercise the patient returned to the sitting position and the oxygen debt was recorded. An investigator wearing a separate hood continuously observed the subject in the Metabolic Chamber during the exercise periods. Two subjects, each with a normal cardiovascular system and of body builds and weights comparable to two of the patients, were exercised under identical conditions to those employed for the patients. The resultant oxygen debts of control subject no. 1 were compared with those of patient C.A., while the debts of subject no. 2 were compared with those of patient S.M.

**Results**

The dietary sodium intake, body weight, venous pressure, periods of drug administration, and days on which oxygen debt measurements were carried out in patients C.A. and S.M. are illustrated in figures 1 and 2. Patient P.F.'s body weight on the days of study is shown in table 1. No notable changes occurred in the patients' subjective conditions, body weights, or venous pressures when digoxin was discontinued or restarted.

During the first period of study, while patient C.A. was receiving digoxin, the oxygen debts following two 10-minute walks were 496 ml. and 433 ml., respectively. During these two studies the oxygen debts averaged 12 per cent of the total excess \( \text{Vo}_2 \) resulting from exercise. During the second period, while receiving the placebo, the resting \( \text{Vo}_2 \) tended to be higher than during the prior period when on digoxin. The oxygen debts rose to 768 ml., 733 ml., and 718 ml., representing, on the average, 22.3 per cent of the total excess \( \text{Vo}_2 \) resulting from exercise. When digoxin was reinstituted, resting \( \text{Vo}_2 \) fell and the oxygen debts fell to 413 ml., 594 ml., and 698 ml., with the oxygen debts averaging 16.3 per cent of the total excess \( \text{Vo}_2 \) resulting from exercise. In addition, the oxygen debt following a shorter (7 min. 40 sec.) walk equaled 1,009 ml. when the patient was not receiving digoxin, and declined to 661 ml. after the glycoside was reinstituted. Control subject no. 1 developed oxygen debts of 427 and 336 ml. respectively during two 10-minute walks and

*Figure 3*

**Block diagram of instrumentation in Metabolic Chamber.**
his oxygen debts averaged 11.0 per cent of the total excess \( V_o_2 \) resulting from exercise (table 1, fig. 5).

Patient P.F. was exercised on a single occasion for 10 minutes while receiving digoxin and developed an oxygen debt of 1,301 ml.; this value represented 10 per cent of the total excess \( V_o_2 \) resulting from exercise. After discontinuation of this medication, the oxygen debt for the same exercise rose to 2,124 and 2,406 ml. on two occasions, with the debts averaging 13.5 per cent of the total excess \( V_o_2 \) resulting from exercise. In addition, the oxygen debt following a shorter period of exercise (7 min. 35 sec.) equaled 1,837 ml. during digoxin administration and rose to 2,461 ml. after the glycoside was discontinued (table 1, fig. 6).

Patient S.M. was exercised for 15 minutes on two occasions while not receiving digoxin and developed oxygen debts of 624 ml. and 686 ml. respectively, with these debts representing, on the average, 12.5 per cent of the total excess \( V_o_2 \) resulting from exercise. During digoxin administration the resting \( V_o_2 \) values were comparable to those obtained during the previous period, and the oxygen debts after exercise declined to 462 ml., 530 ml., and 402 ml. During these three studies the oxygen debts averaged 11.0 per cent of the total excess \( V_o_2 \) resulting from exercise. The normal subject developed debts of 260 ml. and 252 ml. with the oxygen debts averaging 7.5 per cent of the total excess \( V_o_2 \) resulting from exercise. In addition, patient S.M. was exercised both with and without digoxin administration under three other conditions (table 1). Under each condition the oxygen debts after exercise were always lower during digoxin administration (table 1, fig. 7).

**Discussion**

The oxygen debt measured following the
comclusion of exercise represents the summation of instantaneous oxygen deficits accumulated during the entire exercise period. Measurement of this variable is a sensitive technic for assessing the adequacy of the circulatory system, especially when an individual can be employed as his own control. If the delivery of oxygen is only slightly impaired by an inability of the cardiac output to rise adequately during exercise, the circulatory deficit may be difficult or impossible to detect by the measurement of cardiac output alone, but a measurable oxygen debt may accumulate. For example, an increase from 300 to 600 ml. of the oxygen debt incurred during two 10-minute periods of identical exercise represents a rise of 100 per cent and may easily be detected by the methods employed in this study. If it is assumed that the cardiac output is constant during the entire exercise period, the higher oxygen debt would be associated with an oxygen delivery which is only 30 ml. per minute lower during the study in which the oxygen debt was greater. If an arterio-mixed venous oxygen difference during exercise of 12 vol. per cent is assumed, the difference in cardiac outputs during the two periods would be only 250 ml. per minute, a value that is impossible or extremely difficult to measure reliably by the best technics available to the clinical investigator. It was with these considerations in mind that the measurement of the oxygen debt after exercise rather than the more usual approach of measuring cardiac output at rest and during exertion was selected for studying the effects of digitalis.

In 1931, Harrison, Calhoun, and Turley studied the effects of digitalis in a group of
cardiac patients with exertional dyspnea, some of whom also had paroxysmal nocturnal dyspnea. These investigators observed that concomitant with the patients' symptomatic improvement, the ratio of ventilation to vital capacity ('ventilation index') during exertion diminished. Nylin noted that the $V_{O_2}$ measured several minutes after exercise declined following digitalization in a single patient with heart disease and exertional dyspnea.

Although the patients utilized in the present studies had previously experienced congestive heart failure, and although some diminution in cardiac reserve persisted, they were compensated in the absence of digitalis therapy and were able to perform their normal everyday activities without symptoms. Indeed, patient P.F. walked 11½ miles twice daily without discomfort while the studies were being carried out. The administration or withdrawal of digitalis in these patients did not result in any apparent subjective changes or alterations of weight, venous pressure, or of cardiac size, as determined by chest roentgenograms. On the basis of these observations and measurements there was no evidence that the effects of digitalis administration were beneficial. However, detailed and repeated measurements of the absolute oxygen debt after exercise always revealed lower values while the patients were receiving digoxin, although there was considerable variation among individual studies. There was also considerable variation in the total excess $V_{O_2}$ resulting from identical exercise periods in each patient, but the administration of digoxin did not appear to affect this variable. The changes in the oxygen debt were therefore accompanied by declines in the ratio of the oxygen debt to the total excess $V_{O_2}$ resulting from exercise. However, in spite of the reduction of the oxygen debt during digoxin administration, it was apparent that in two of the three patients studied, the debts did not decline to the levels observed in subjects with normal cardiovascular systems (figs. 5 and 7). These reductions of the oxygen debts after exercise without concomitant changes in the total oxygen cost of exercise are consistent with the hypothesis that in these three patients digitalis improved the delivery of oxygen to the systemic vascular bed during exertion, and thus permitted the oxygen delivery to meet the oxygen requirements in a more satisfactory fashion. These observations suggest strongly that, in the three patients studied, the digitalis glycoside resulted in significant improvement of over-all circulatory function in spite of the absence of any apparent clinical benefits. From a therapeutic point of view it therefore appears that at least some patients with enlarged hearts without heart failure are benefited by digitalis administration.

Summary

Three patients with acquired valvular heart disease and cardiac enlargement who were able to perform normal everyday activity without difficulty in the absence of digitalis therapy were exercised while receiving a placebo and again while receiving digoxin. Digoxin administration did not produce a significant change in body weight or in the subjective condition of the individuals. Varying degrees of exercise were performed on a treadmill in a Metabolic Chamber and oxygen consumption was measured continuously before, during, and after the period of exercise, utilizing a continuous gas flow paramagnetic oxygen analyzer. The oxygen debt that developed during digoxin administration was compared to that observed during placebo administration.

In all patients the oxygen debt was smaller during the period of digoxin administration, although the external work performed was identical. In the first patient, following a 7-minute walk, the oxygen debt was 53 per cent more and following a 10-minute walk it averaged 40 per cent more while not receiving digoxin than when receiving this drug. In the second subject the oxygen debt following a 7-minute walk was 34 per cent more and following a 10-minute walk it averaged 74 per cent more when he was not receiving digoxin than when receiving this drug. In the third subject the oxygen debts were 46 per cent and 41 per cent greater following 10- and 15-
minute walks respectively, when she was not receiving digoxin.

The accumulation of a smaller oxygen debt following exercise while these subjects were receiving digoxin indicates that the functional status of their circulatory system was improved by the drug. It would appear that digitalis administration is beneficial to at least some patients who have cardiac disease and enlarged hearts and some decrease in cardiac reserve without signs or symptoms of heart failure.

References
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Circulation. 1963;27:397-405
doi: 10.1161/01.CIR.27.3.397

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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