Effects of Digoxin on Exercise Capacity and Right Ventricular Function during Exercise in Chronic Airflow Obstruction*


We evaluated 12 patients with stable chronic airflow obstruction (CAO) and no clinical evidence of left ventricular disease to determine the effects of oral digoxin on exercise capacity (V̇O₂ max) and on right ventricular pump function during exercise. In this randomized, double blind, placebo controlled, cross-over study, patients performed exercise tests and underwent measurement of ejection fractions after two weeks of therapy with oral digoxin (0.25 mg/day) and after two weeks of placebo. Incremental upright exercise testing to a symptom-limited maximum was performed on a cycle ergometer. Right and left ventricular ejection fractions (RVEF, LVEF) were obtained in the supine position at rest and at approximately 75 percent of the maximum workload by gated equilibrium radionuclide angiography. All patients had abnormal right ventricular function, manifested either by a low resting RVEF (<45 percent) or a subnormal response to exercise (<5 percent increase). The small increases in RVEF with digoxin (mean ± SE) at rest (44 ± 5 vs. 41 ± 4 percent) and during exercise (46 ± 4 vs. 44 ± 3 percent) did not achieve statistical significance. With digoxin, small increases in exercise duration (10.0 ± 1.5 vs. 9.0 ± 1.4 min), maximum workload achieved (48 ± 6 vs. 42 ± 5 W), V̇O₂ max (0.85 ± 0.06 vs. 0.81 ± 0.06 L/min), and oxygen-pulse (O₂-P) (6.6 ± 0.5 vs. 6.3 ± 0.4 ml/beat) occurred. Only the increase in O₂-P was significant (p < 0.05). From this study we conclude that digoxin does not significantly improve exercise capacity in severe chronic airflow obstruction with impaired right ventricular function, nor does it improve RVEF either at rest or during supine submaximal exercise.

The role of digitalis in the treatment of severe chronic airflow obstruction (CAO) with concomitant right ventricular dysfunction has been debated for years. Studies of the hemodynamic effects of the drug at rest have been conflicting. Advances in radionuclide imaging techniques now allow evaluation of right and left ventricular ejection fractions (RVEF, LVEF) at rest and during exercise. A recent well-designed study utilizing radionuclide techniques concluded that resting right ventricular function was not improved by digoxin in patients with pulmonary heart disease unless concomitant left ventricular dysfunction was also present.

The hemodynamic effects of digitalis during exercise in patients with CAO are not well delineated. Interpretation of the few available studies is limited by problems of study design. The nature and severity of the underlying pulmonary disease have usually not been adequately described. The studies have not been randomized, blinded, placebo-controlled investigations. Evaluation has been performed only after a single intravenous dose of a digitalis preparation, and often the number of patients studied was small.

The RVEF often decreases or fails to show the normal increase during exercise in CAO even in patients without overt clinical evidence of right ventricular failure. Whether oral digoxin therapy attenuates the decrease in RVEF with exercise or normalizes the RVEF response in CAO is unknown, as is the effect of digoxin on overall exercise capacity. Although exercise tolerance is generally felt to be limited primarily by airway mechanics, recent investigations have raised questions about the possible role of abnormal pulmonary hemodynamics in the limitation of exercise performance. The purpose of this study was to determine the effects of administration of oral digoxin on exercise capacity and on right ventricular function during exercise in patients with severe CAO.

Materials and Methods

Patients

Twelve patients with stable severe CAO whose exercise capacity was limited by dyspnea were studied. Demographic data are summarized in Table 1. Patients with known coronary artery disease, evidence of left ventricular enlargement on chest radiographs, clinical evidence of cardiac valvular disease, or patients with a...
### Table 1—Demographic Data (n = 12, mean ± SE)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo Mean ± SE</th>
<th>Digoxin Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>62 ± 2</td>
<td></td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>0.93 ± 0.08</td>
<td></td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.51 ± 0.14</td>
<td></td>
</tr>
<tr>
<td>FEV/FVC</td>
<td>0.38 ± 0.03</td>
<td></td>
</tr>
<tr>
<td>FRC, % pred</td>
<td>249 ± 13</td>
<td></td>
</tr>
<tr>
<td>RV, % pred</td>
<td>323 ± 21</td>
<td></td>
</tr>
<tr>
<td>TLC, % pred</td>
<td>142 ± 6</td>
<td></td>
</tr>
<tr>
<td>Dco, % pred (n = 10)</td>
<td>41 ± 3</td>
<td></td>
</tr>
</tbody>
</table>

History of previous digitalis administration were excluded, as were individuals with other medical problems that precluded maximal exercise testing. Nine patients had ECG evidence of right axis deviation and/or signs of right ventricular hypertrophy. One patient had a clinical history of right ventricular failure manifested by pedal edema and was being treated with a diuretic. All patients were taking oral theophylline preparations and inhaled beta adrenergic agents; nine were taking oral beta adrenergic agents. Medications were not withheld on the study days; all were continued at stable doses throughout the entire study period. Written informed consent approved by the Human Studies Committee was obtained from each patient.

### Study Protocol

Prior to the study, a cycle ergometer test was performed to familiarize the patient with the laboratory, and pulmonary function test results were obtained. Then in randomized, double-blind, cross-over fashion, patients were evaluated on two study days: 1) after two weeks of therapy with oral digoxin (0.25 mg/day), and 2) after two weeks of receiving a placebo. There was no washout period between the two study periods. Digoxin levels were obtained in each patient on each study day. With the active drug, the digoxin level was 1.02 ± 0.10 ng/ml. On the placebo day, digoxin levels were undetectable (<0.5 ng/dl). On each study day, patients underwent spirometry, performed a cycle ergometer exercise test, and underwent measurement of ejection fractions.

### Pulmonary Function Tests

Spirometric measurements were made with a 12-liter dry rolling seal spirometer (CPI 231). Lung volumes were measured by body plethysmography (W. E. Collins). The diffusing capacity (Dco) was measured by the single-breath method (CPI 451). The normal values of Knudsen et al. and Cotes and Hall were utilized.

### Exercise Tests

Progressive exercise was performed to a symptom-limited maximum on an electrically-braked cycle ergometer (Gould Godart) with increases in workload of 15-20 watts every four minutes. Heart rate (fc), respiratory rate (fb), and analysis of expired gas were obtained at rest and during the last minute of each workload. When the patient was unable to complete the full four minutes at the highest workload, he was instructed to signal prior to complete exhaustion so that data could be collected before cessation of exercise. Heart rate was recorded by electrocardiography (Statham). Respiratory rate was obtained from the end-tidal Pco₂ tracing and used with the expired minute volume to determine tidal volume (Vt). Mixed expired gas was collected in a 120 liter meteorologic balloon. The volume was measured in a 120 liter Tissot gasometer with correction for the aliquots removed for gas analysis. Tidal volume was corrected for the dead space (110 ml) of the two-way breathing valve (Hans-Rudolph 2700). Analysis of mixed expired oxygen (FEO₂) and carbon dioxide (FECO₂) fractions was performed with gas analyzers (Beckman OM-11 and LB-2) that were calibrated immediately before each test with appropriate mixtures of O₂, CO₂, and N₂.

Rates of CO₂ elimination (VeCO₂) and O₂ uptake (Vo₂) were calculated from measurements of expired minute volume (Ve) and the compositions of inspired and expired gas. The respiratory exchange ratio (r) was calculated as the ratio of these two values. The oxygen pulse (O₂-P) value was calculated as Vo₂/fc (ml/beat).

### Radionuclide Data Processing

Electrocardiogram Ejection fractions for right and left ventricle were calculated using the MUGA program of Medical Data Systems. Where exercise images contained insufficient counts for easy processing, smoothing or filtering with a simple five-point Gaussian filter was carried out to permit easier edge definition.

### Data Analysis

Statistical analysis was performed using Student's t test for matched pairs. Differences were considered statistically significant when p < 0.05 (two-tailed test). Data are reported as mean ± 1 SE.

### Results

Resting ventilatory, cardiac, and metabolic data are summarized in Table 2. Digoxin did not significantly alter any of these measurements. The FEV₁ and FVC were not altered by digoxin.
**Table 3—Maximum Exercise Data (n = 12)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo Mean ± SE</th>
<th>Digoxin Mean ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise duration, min</td>
<td>9.0 ± 1.4</td>
<td>10.0 ± 1.5</td>
</tr>
<tr>
<td>Workload, watts</td>
<td>42 ± 5</td>
<td>48 ± 6</td>
</tr>
<tr>
<td>fc, beats/min</td>
<td>128 ± 5</td>
<td>129 ± 5</td>
</tr>
<tr>
<td>BP syst, mm Hg</td>
<td>169 ± 3</td>
<td>172 ± 5</td>
</tr>
<tr>
<td>BP diast, mm Hg</td>
<td>101 ± 4</td>
<td>95 ± 4</td>
</tr>
<tr>
<td>V̇max, L/min, BTSP</td>
<td>31.0 ± 2.1</td>
<td>30.8 ± 2.2</td>
</tr>
<tr>
<td>V̇, L, BTSP</td>
<td>1.02 ± .08</td>
<td>1.07 ± .07</td>
</tr>
<tr>
<td>fβ, breaths/min</td>
<td>35 ± 3</td>
<td>36 ± 4</td>
</tr>
<tr>
<td>V̇O₂max, L/min, STPD</td>
<td>0.81 ± 0.06</td>
<td>0.85 ± 0.06</td>
</tr>
<tr>
<td>VCO₂max, L/min, STPD</td>
<td>0.81 ± 0.07</td>
<td>0.87 ± 0.08</td>
</tr>
<tr>
<td>r</td>
<td>1.00 ± 0.02</td>
<td>1.02 ± 0.03</td>
</tr>
<tr>
<td>V̇E/V̇O₂</td>
<td>43 ± 2</td>
<td>42 ± 2</td>
</tr>
<tr>
<td>V̇E/VCO₂</td>
<td>43 ± 2</td>
<td>42 ± 2</td>
</tr>
<tr>
<td>O₂-P, ml/beat</td>
<td>6.3 ± 0.4</td>
<td>6.6 ± 0.5*</td>
</tr>
</tbody>
</table>

*p < 0.05

**Exercise Capacity**

Maximum exercise data are summarized in Table 3. The V̇O₂max with placebo was .81 ± .06 L/min and the maximum workload achieved was 42 ± 5 watts. The patients achieved 91 ± 5 percent of their maximum predicted ventilation and 75 ± 3 percent of their maximum predicted heart rate. Digoxin did not affect ventilation, breathing pattern, ventilatory efficiency, heart rate or blood pressure at exhaustion. Exercise duration, maximum workload, V̇O₂ max, and O₂-P all showed small increases with digoxin. However, only the increases in O₂-P achieved significance (p < 0.05).

**Resting Ventricular Function**

With placebo the mean resting RVEF of the 12 patients was 41 ± 4 percent and resting LVEF was 59 ± 3 percent. Eight patients had abnormal resting RVEF values (<45 percent). Nine patients had normal LVEF values (≥50 percent); LVEF was only minimally decreased in the three remaining patients (47, 48 and 49 percent, respectively). In two patients, the ejection fractions of both ventricles were abnormal. Digoxin did not significantly improve the resting ejection fraction of either ventricle (Fig 1, left panel).

**Exercise Ventricular Function**

With placebo, the mean exercise RVEF was 44 ± 3 percent. Seven patients had an abnormal exercise response (<5 percent increase). The four patients with normal resting RVEF all had abnormal exercise responses. Thus, with placebo all patients had RV dysfunction as manifested by either an abnormal resting RVEF or an abnormal response to exercise. The mean exercise LVEF was 63 ± 4 percent. In six patients, a normal (>5 percent) increase occurred with exercise. In one additional patient, the high resting LVEF (69 percent) was unchanged. In the remaining five patients, the LV response to exercise was abnormal. Seven patients had abnormal LV function, manifested by either an abnormal resting LVEF or an abnormal LVEF response to exercise (<5 percent). Digoxin resulted in small increases in exercise RVEF (from 44 ± 3 to 46 ± 4 percent) and exercise LVEF (from 63 ± 4 to 65 ± 3 percent); neither of these changes achieved significance (Fig 1, right panel). Thus, digoxin did not significantly alter the group mean ejection fractions of either ventricle under resting or exercise conditions, nor was the overall exercise performance of the group significantly improved with the drug.

**DISCUSSION**

Oral digoxin therapy did not improve resting RVEF in our patients with severe CAO. Our findings are similar to those reported in a previous study in which abnormal resting RVEF in CAO improved with digoxin treatment only in the four cases when the LVEF was initially low and normalized with drug therapy. In the current study, the LVEF in only one of three patients with initially abnormal LVEF normalized with digoxin. Possible explanations for this difference include a higher mean digoxin level and longer duration of therapy in the former study and the fact that the greatest improvement in LVEF seen in the previous study occurred in the two patients with markedly decreased baseline LVEF. In contrast, our three patients had minimally abnormal values. The incidence of abnormal resting LVEF was similar in the two studies. We found a higher incidence of abnormal left ventricular exercise reserve than previously reported. This is probably because our patients had more severe CAO.

The potential role of digitalis in the treatment of cor pulmonale is controversial. The results of earlier
studies, some of which have shown evidence of hemo-
dynamic improvement with digoxin, have often been
difficult to evaluate, due to problems of study design.
Our study, along with the study of Mathur et al,12
suggests that no significant improvement in isolated
right ventricular resting dysfunction results from oral
digoxin therapy in stable severe CAO.

Less information is available regarding the effects
of digitalis during exercise in CAO. The RVEF often
decreases or fails to show the normal exercise response
in many of these patients.9 Digoxin might attenuate
this deterioration in RV function with exercise or even
normalize the exercise response. It has been shown that
RVEF during exercise does improve when supplemental
oxygen is administered.10 We found that no signifi-
cant change occurred in RVEF with digoxin during
submaximal exercise. Our results are in agreement
with and expand upon two previous studies,3,4 both of
which failed to show a consistent decrease in right ven-
tricular filling pressure or an increase in stroke volume
or cardiac output during exercise. These studies evalu-
ated the effects of a single intravenous dose of digitalis.
A placebo-controlled, randomized, double blind pro-
ocol was not used. Our patient population consisted
only of patients with severe CAO in contrast to the
other studies which evaluated patients with a variety of
underlying pulmonary disorders. A recent report also
failed to show any improvement in the calculated
cardiac stroke volume following digoxin therapy in a
group of young subjects with cystic fibrosis.19

Most previous studies have evaluated exercise per-
formance at a single workload. Our incremental exer-
cise protocol allowed us to evaluate changes in max-
imum exercise capacity. Digoxin did not significantly
improve the mean VO_{2,\text{max}} of our patients. Digoxin has
also failed to improve the maximum workload in cystic
fibrosis.19

Five patients ("improvers") had a >10 percent
improvement in VO_{2,\text{max}} with digoxin as compared to
placebo (Fig 2). This subgroup did not differ from
the remaining patients with respect to severity of airway
obstruction, baseline exercise capacity, cardiac or
ventilatory reserve at exhaustion, or baseline ejection
fractions at rest or during exercise, although there was
a trend for a higher baseline RVEF in those who
improved. Even in this subgroup of five patients,
digoxin did not significantly improve RVEF or LVEF at
rest or at Emax (Fig 3). Thus, improved exercise
performance was not related to increases in exercise
RVEF.

Several factors may have been responsible for the
lack of effect of digoxin. Small improvements in exer-
cise capacity or ventricular function could have been
undetected because of the limited number of patients
studied. It is possible that the dosage given was
insufficient. However, the oral daily dose of 0.25 mg
did result in therapeutic digoxin levels. Patients with

---

**Figure 2.** Group mean and individual VO_{2,\text{max}} data with and
without digoxin. Broken lines represent patients who had a ≥10 percent increase in VO_{2,\text{max}} while on digoxin. Open circles represent
mean data.

**Figure 3.** Mean right and left ventricular ejection fractions at rest
and during exercise with and without digoxin in the five "improvers." Vertical bars represent 1 SE.
CAO are known to be more likely to develop digitalis toxicity and we doubt that larger doses would have altered our conclusions. We did not have a drug washout period in our study design, as increasing the total length of the study would have increased the chances of exacerbations occurring between the two arms of the study. It is possible that some digoxin effect was present during the placebo period in patients who took the active drug first. This appears unlikely, since at least 14 days elapsed between the study days, our patients all had normal renal function, and digoxin levels were all undetectable (<0.5 ng/dl) on the placebo day. Heart rate at exhaustion was similar in both phases suggesting comparable patient effort.

Slight improvement in RV contractility, too subtle to be detected by radionuclide techniques, may have occurred with digoxin, since ejection fraction measurements are affected by preload and afterload, as well as by myocardial contractility. If so, this may have been counterbalanced by an increase in pulmonary vascular resistance or hypoxemia, both of which have been reported with digoxin therapy.

It is doubtful that a population of patients with more clinically overt right heart failure would have shown improvement with digoxin, since the trend was for "improvers" to have better, rather than worse, right ventricular function. Concurrent treatment of patients with theophylline and beta adrenergic agents may have masked a potential digoxin effect on ventricular function. Since digoxin would be used clinically in patients already taking bronchodilators, we believe it is more important for the clinician to know if the drug is effective when given in addition to bronchodilators.

Since ejection fractions did not improve with digoxin, this study does not answer the question of whether an improvement in right or left ventricular function would improve exercise capacity in this patient group. It is likely that since our patients closely approached their predicted maximum ventilation at exhaustion, their exercise capacity was limited predominantly by airway mechanics. If this is the case, improved cardiac function might not have any beneficial effect on exercise capacity.

We conclude that digoxin does not improve maximum exercise capability and does not result in improved right ventricular function in patients with severe stable CAO. Thus, it should not be used in these patients for that purpose.

ACKNOWLEDGMENTS: The authors thank Karen LoPresti and Kay Lines for performing the pulmonary function testing, Marian Berman for preparing the illustrations, Kenneth Lyons, M.D. for assistance with the radionuclide studies, and Barbara Ikeda and Sandy Light for preparing the manuscript. This work was supported by the Research Service of the Veterans Administration.

REFERENCES

1 Ferrer MI, Harvey RM, Cathcart RT, Webster CA, Richards, Jr DW, Cournand A. Some effects of digoxin upon the heart and circulation in man. Circulation 1950; 1:161-86
5 Vatner SF, Braunwald E. Effects of chronic heart failure on the inotropic response of the right ventricle of the conscious dog to a cardiac glycoside and to tachycardia. Circulation 1974; 50:728-34
10 Olvey SK, Reduto LA, Stevens PM, Deaton WJ, Miller RR. Effect of oxygen upon exercise response. Chest 1980; 78:4-9

CHEST / 85 / 2 / FEBRUARY, 1984