Indications for Acute and Chronic Digitalis Administration in Heart Failure

Mihai Gheorghiade
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Mihai Gheorghiade, MD*

Although digitalis glycosides were introduced for the treatment of cardiac disorders almost 200 years ago, doubt persists regarding the role of these inotropic agents in the treatment of heart failure patients with a normal sinus rhythm. Cardiac glycosides are undoubtedly highly effective in controlling the ventricular response in the presence of atrial fibrillation, and thereby enhance cardiac performance. Past experimental and clinical data have shown that various digitalis preparations improve ventricular function when the drug is acutely administered and indices of myocardial contractility are measured (1-3). However, a dissociation may exist between the effects of digitalis on indices of ventricular contractility (systolic time intervals, measurements of rate of rise of left ventricular pressure, or direct measurement of myocardial contractile force) and overall cardiac pump performance, which is expressed as the relationship between left ventricular filling pressure and cardiac output. Although indices of contractility can be shown to increase with acute administration of digitalis, significantly improved pump performance does not always occur (4-7).

The clinical use of digitalis should be reexamined for several reasons. Concerning the benefit of digitalis, the literature is somewhat confusing because authors fail to distinguish acute and chronic effects of the drug. Scant information is available demonstrating the relative effect of cardiac glycosides compared to the combination of diuretics and vasodilators in the treatment of heart failure. A troubling risk of toxicity remains because of the narrow borderline between the therapeutic and toxic effects; toxic manifestations of digitalis therapy still comprise some of the most prevalent adverse drug reactions encountered in clinical practice (8). Except for the use of digitalis in atrial fibrillation, it is uncertain who benefits from digitalis. Cardiac glycosides purportedly increase mortality when administered soon after myocardial infarction (9,10). In patients initially treated with diuretics to maintain dry body weight, no added benefit from digitalis is observed (11). Newer inotropic drugs and vasodilators have been shown to be effective in treating heart failure patients and may be superior to digitalis (12).

Acute Use of Cardiac Glycosides

Digitalis in acute myocardial infarction

Although digitalis therapy in patients with acute myocardial infarction has been employed since 1912 (13), controversy persists regarding the indications and use of digitalis in such patients. Investigation of the effects of digitalis on cardiac function in patients having congestive heart failure in both the acute and convalescent phases of myocardial infarction yields conflicting and inconsistent data (14,15).

If digitalis is administered to patients in sinus rhythm during the acute phase of myocardial infarction with either absent or mild clinical heart failure, little hemodynamic benefit can be expected (16,17). In contrast, digitalis therapy is of value in this setting when atrial fibrillation is present; benefit is obtained by control of the ventricular response to the tachyarrhythmia. Digitalis might be of benefit when signs of heart failure are accompanied by an S3 gallop, significant cardiomegaly, and elevation of the left ventricular end-diastolic pressure. However, even in this setting, few studies in humans are available that suggest a significant improvement in left ventricular performance with digitalization (18). Forrester et al (19), Lipp et al (20), and Goldstein et al (21) reported no occurrence of hemodynamic improvement in their patients, whereas Hodges et al (22) reported an improvement in only four of the ten patients studied. Rahimtoola et al (23) reported an improvement in left ventricular filling pressure without a significant change in cardiac index when ouabain was administered within 48 hours of acute myocardial infarction. In fact, rapid intravenous administration of digitalis may be detrimental, which is perhaps related to its acute peripheral constrictor effect (16).

Infarct size—Varankov and associates (24) examined the effect of acetylstrophanthidin on the rate of creatine phosphokinase (CK) efflux in 59 patients with acute myocardial infarction. They found an accelerated release of CK in the plasma of these patients, with an evolving uncomplicated infarction, and concluded that digitalis administration may have adversely increased infarct size.

Arrhythmogenic effect—Whether patients with myocardial infarction are more sensitive to the arrhythmogenic effects of digitalis has not been definitively ascertained. Reicansky and colleagues (25), using a double-blind randomized protocol, found no difference in the incidence of rhythm disturbances between digoxin-treated and control patients with acute myocardial infarction. An increased susceptibility to arrhythmias in the presence of digitalis intoxication has been observed in experimental models following acute coronary ligation (26,27).

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Therapeutic approach—Patients in sinus rhythm with mild to moderate heart failure (bisibular rales, S3 gallop, and upper zone pulmonary venous redistribution on chest roentgenogram) secondary to acute myocardial infarction should receive diuretics alone or a combination of a diuretic and a vasodilator as the first step in their management. Intravenous nitroglycerin or nitroprusside appears to be highly effective in reducing the left ventricular end-diastolic pressure and improving cardiac output in such patients. The addition of digoxin to nitroprusside may increase the cardiac output more than nitroprusside alone in patients with heart failure complicating myocardial infarction, but it does not produce any further decrease in pulmonary capillary wedge pressure (28).

Cardiogenic shock—The beneficial effects of digitalis have been examined in the setting of cardiogenic shock, in which marked hypotension is observed in association with an elevated left ventricular filling pressure. The prognosis of patients with cardiogenic shock appears to be unaltered following digitalis administration (17). Clinical studies have reported that the drug does not appear to have any beneficial effect on left ventricular function (29-31). Cohn and associates (29) demonstrated that the early pressor effect of intravenously administered ouabain is deleterious in patients with cardiogenic shock. Digitalis adds little when compared with the more potent inotropic agents such as dobutamine (23).

Acute digitalization in patients with chronic heart failure
Not all patients with severe and chronic heart failure will show an improvement in hemodynamics after the administration of intravenous digitalis (32-35). Selzer and Malmborg (32) were unable to predict which patients would respond to acute digitalis administration (only 60% of their patients had a significant hemodynamic response). Yankopoulos et al (33) found that patients only in the New York Heart Association’s functional class III or IV responded to intravenous ouabain, whereas in Cohn et al’s series (34) four of eight patients had hemodynamic deterioration which coincided with an increase in total systemic vascular resistance following intravenous digoxin. Ribner et al (35), however, recently reported hemodynamic benefit with intravenous digoxin in all 11 patients with alcoholic or idiopathic cardiomyopathy.

Therapeutic approach—Because patients admitted with an exacerbation of chronic heart failure can be compensated with diuretics, vasodilators, and intravenous inotropic agents (i.e., dobutamine and amrinone), digitalis should be reserved for only those patients with heart failure complicated by atrial fibrillation with a rapid ventricular response or those who have continuous signs and symptoms of congestive heart failure despite optimal doses of diuretics and vasodilators.

Chronic Use of Digitalis Glycosides
Digitalis in chronic heart failure
The value of long-term chronic oral digoxin therapy in chronic heart failure patients is controversial. Benefits have not been definitively demonstrated, and the risk of toxicity is always present. We prospectively evaluated the clinical and hemo-dynamic effects of digoxin discontinuation in patients with normal sinus rhythm and congestive heart failure (36). We sought to determine changes not only in symptoms and physical findings after discontinuation of the drug but also in left ventricular function and exercise capacity. The major difference in our study design from that employed in previous studies was to maximize therapy with diuretics and vasodilator drugs before discontinuing digoxin.

Materials
The study group patient population was homogeneous in that all had documented chronic heart failure secondary to coronary artery disease. Twenty-four consecutive patients were prospectively studied. All 24 patients were men with a mean age of 60 years (range of 42 to 80 years). No patient had a history of atrial tachyarrhythmia. The indication for initiating long-term digoxin therapy in the study cohort was the presence of clinical and/or radiographic evidence of congestive heart failure. None of the patients had congestive heart failure precipitated solely by recurring episodes of acute ischemia. Before discontinuing maintenance digoxin therapy, patients received the drug for two to 180 months (average 39 months). Plasma digoxin levels were obtained six to eight hours after the last digoxin dose and ranged from 0.8 to 2.2 ng/mL (1.2 ± 0.3 ng/mL, mean ± standard deviation). The digoxin dosage was not adjusted to achieve a therapeutic serum level, and only patients with a chronic therapeutic level were entered into the study. Before digoxin withdrawal, 21 patients (88%) were receiving diuretic and/or vasodilator therapy for congestive heart failure (Table 1). A total of 20 patients (83%) were receiving diuretics; 16 (66%) were receiving vasodilators; 14 were receiving both diuretics and vasodilators; and two patients were taking a long-acting nitrate preparation and another vasodilator.

Concurrent therapy for congestive heart failure or angina pectoris was not altered during the follow-up period except in two patients in whom isosorbide dinitrate therapy was initiated because of symptoms consistent with worsening angina pectoris and no change in the status of their heart failure.

Methods
Baseline studies were obtained while patients were still receiving maintenance digoxin therapy and before drug discontinuation. These studies consisted of the following: a complete cardiovascular history, physical examination including measurement of body weight, a resting 12-lead electrocardiogram, a


Table 1
Maintenance Diuretic and Vasodilator Therapy Before and After Digoxin Withdrawal

<table>
<thead>
<tr>
<th>Diuretics/Vasodilators</th>
<th>No. of Patients</th>
<th>Dose Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretics:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>12</td>
<td>55 mg (20 to 80 mg)</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>8</td>
<td>50 mg (25 to 100 mg)</td>
</tr>
<tr>
<td>Vasodilators:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>2</td>
<td>93 mg (40 to 200 mg)</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>13</td>
<td>66 mg (40 to 120 mg)</td>
</tr>
<tr>
<td>Nitroglycerin ointment</td>
<td>3</td>
<td>2 in (2 to 4 in)</td>
</tr>
</tbody>
</table>
standard posteroanterior chest roentgenogram, a resting gated cardiac blood pool scan, and a symptom-limited treadmill exercise test. Serial exercise testing as a method of assessment was introduced midway into the study. The last 14 consecutive patients were studied in this manner.

Each patient was assigned a heart failure score based on symptoms, signs, and findings on chest roentgenography. Each of the following was assigned one point when present: dyspnea on exertion, paroxysmal nocturnal dyspnea, sinus tachycardia, jugular venous distention, pulmonary end-inspiratory rales, an S3 gallop, peripheral edema, a cardiothoracic ratio > 0.5, radiographic interstitial edema, alveolar changes, pulmonary venous hypertension, and pleural effusion. The score ranged from zero, reflecting an absence of the 12 variables, to 12, representing the presence of each of the listed findings. After completing a baseline evaluation, digoxin was discontinued in all patients.

### Statistical analysis

Values are expressed as mean ± standard error of the mean. Comparison between baseline and digoxin withdrawal studies in individual patients was made using the paired t-test, and comparison between groups was performed using analysis of variance.

### Results

One month after digoxin withdrawal no significant difference was observed in resting heart rate; systolic, diastolic, or mean blood pressure; body weight; or duration of symptom-limited treadmill exercise (Table 2). Also, no difference was observed in cardiac symptoms, physical findings, cardiothoracic ratio, radiographic signs of pulmonary congestion, resting radio-

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**Table 2**

<table>
<thead>
<tr>
<th>Measurements</th>
<th>On Digoxin</th>
<th>Off Digoxin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>75 ± 2</td>
<td>76 ± 2</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>122 ± 4</td>
<td>125 ± 3</td>
</tr>
<tr>
<td>Diastolic</td>
<td>73 ± 2</td>
<td>72 ± 2</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>78.3 ± 2.7</td>
<td>78.2 ± 2.7</td>
</tr>
<tr>
<td>Cardiothoracic ratio</td>
<td>0.53 ± 0.01</td>
<td>0.53 ± 0.01</td>
</tr>
<tr>
<td>Exercise capacity* (min)</td>
<td>6.1 ± 0.8</td>
<td>7.2 ± 0.9</td>
</tr>
</tbody>
</table>

*Exercise testing conducted in 14 consecutive patients. Values are expressed as mean ± standard error of the mean.
nuclide ejection fraction, or heart failure score compared with the baseline evaluation gathered during chronic maintenance digoxin therapy. Individual values for the heart failure score before and after digoxin withdrawal are shown in Fig 1. The majority of the patients (67%) had cardiomegaly, as defined by a cardiothoracic ratio greater than 0.5. One month after digoxin discontinuance the cardiothoracic ratio was unchanged compared with the baseline measurements (Fig 2).

Left ventricular ejection fraction data are summarized in Fig 3. Both individual and mean values with and without digoxin therapy are shown. Even in patients with an ejection fraction of < 0.35, no significant differences were noted between the “on” and “off” digoxin periods (Fig 4).

**Discussion**

Our study shows that cessation of oral maintenance digoxin therapy for one month in a group of 24 men in sinus rhythm with documented coronary artery disease and compensated congestive heart failure has little adverse effect. It must be emphasized that 88% of the patients were receiving diuretic and/or vasodilator therapy concurrent with digoxin discontinuation. One of the potential hazards of discontinuing digoxin in patients with chronic congestive heart failure is the development of supraventricular tachyarrhythmias. No patient in our study developed such rhythm disturbances.

The studies reported in the literature concerning the effect of digitalis withdrawal in patients having heart failure are conflicting, primarily because of different patient populations and whether maintenance diuretic and/or vasodilator therapy was used. Investigators have found that digitalis therapy could be discontinued without adverse effects in 50% to 100% of patients with heart failure and sinus rhythm (36–47) (Table 3). Considerable differences exist between the studies regarding the age of the patients (37,38), the etiology of heart failure (46), and serum digoxin concentration (43). Populations studied ranged from those without heart failure (42) through compensated (45) to overt heart failure (44). In some studies the indications for digitalization were unclear (37,38,47). In the report by Dobbs et al (40) the deterioration associated with digitalis withdrawal was manifested by an increase in sodium and water retention. Decompensation might not have occurred if concomitant diuretic and/or vasodilator therapy had been instituted and maximized before digitalis discontinuation (36). McHaffie et al (11) could not detect a symptomatic improvement when digitalis was given to patients with heart failure who achieved a dry body weight

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Fig 3—Radionuclide left ventricular ejection fraction during chronic maintenance digoxin therapy and at one month of digoxin discontinuation. NS = not significant. (From Gheorghiade M, Beller GA. Effects of discontinuing maintenance digoxin therapy in patients with ischemic heart disease and congestive heart failure in sinus rhythm. Am J Cardiol 1983;51:1243-50. Reprinted with permission.)

Fig 4—Left ventricular ejection fraction on and off digoxin. (From Gheorghiade M, Beller GA. Effects of discontinuing maintenance digoxin therapy in patients with ischemic heart disease and congestive heart failure in sinus rhythm. Am J Cardiol 1983;51:1243-50. Reprinted with permission.)
while on diuretic therapy. Furthermore, no significant hemodynamic benefit was noted in response to various digitalis preparations (48-50) in heart failure patients compensated with diuretics and/or vasodilators.

**Therapeutic approach**

The clinical benefit of chronic digitalis administration to patients with chronic heart failure and sinus rhythm who are already receiving diuretic and vasodilator agents is still unclear. Since digitalis has a narrow therapeutic-toxic ratio, it would seem prudent to first treat these patients with diuretics and vasodilators. When symptoms or clinical signs of heart failure, including an S3 gallop (46), persist despite optimal diuretic and vasodilator therapy, digitalis should be added. Digitalis therapy is beneficial to patients who have any form of heart disease with underlying atrial fibrillation or who are prone to episodes of supraventricular tachyarrhythmias.

In patients already on chronic maintenance digitalis therapy, who are well compensated and do not have a third heart sound or history of atrial fibrillation, an attempt should be made to discontinue the glycoside. Digitalis therapy should be avoided or at least used with extreme caution in patients on quinidine therapy or in those with advanced age, cardiac amyloidosis, renal failure, and severe pulmonary disease. Such patients have an increased probability of toxic side-effects at any given dose. Because chronic digoxin therapy in patients with a recent myocardial infarction has little hemodynamic benefit, does not appear to increase survival (51-53), and may actually be associated with increased mortality and sudden death in certain populations (9,10), it would be prudent to restrict its use to only those patients with atrial fibrillation or those not responding to diuretics and vasodilators.

In conclusion the following two points should be remembered. Acute digitalization is of little or no value in controlling signs and symptoms in patients with acute or chronic heart failure and should be reserved for those patients presenting in atrial fibrillation with a rapid ventricular response. Maintenance digitalis therapy should be used only in the presence of atrial fibrillation or in patients whose signs and symptoms of heart failure persist despite diuretic and vasodilator treatment and who have a third heart sound.

**References**

5. Stewart HI, Cohn AE. Studies on the effect of digitalis on the output of blood from the heart. III. J Clin Invest 1932:2:917-55.

**Table 3**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Sample Size</th>
<th>Indications for Digitalization</th>
<th>Serum Glycoside Levels</th>
<th>Follow-up Period in Months</th>
<th>Clinical Deterioration No. (%)</th>
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<tbody>
<tr>
<td>Starr &amp; Luchi (37)</td>
<td>1969</td>
<td>11</td>
<td>U</td>
<td>No</td>
<td>1</td>
<td>0 (0)</td>
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<tr>
<td>Dall (38)</td>
<td>1970</td>
<td>80</td>
<td>U</td>
<td>No</td>
<td>3</td>
<td>21 (26)</td>
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<tr>
<td>Fonrose et al (39)</td>
<td>1974</td>
<td>31</td>
<td>CHF</td>
<td>Yes</td>
<td>4</td>
<td>16 (52)</td>
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<tr>
<td>Dobbs et al* (40)</td>
<td>1977</td>
<td>46</td>
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<td>Yes</td>
<td>1.5</td>
<td>16 (35)</td>
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<tr>
<td>Hull &amp; Krakauer &amp; Petersen (41)</td>
<td>1977</td>
<td>18</td>
<td>CHF</td>
<td>Yes</td>
<td>3</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Johnston &amp; McDevitt (43)</td>
<td>1979</td>
<td>22</td>
<td>U</td>
<td>Yes</td>
<td>3 to 6</td>
<td>6 (27)</td>
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<tr>
<td>Arnold et al (44)</td>
<td>1980</td>
<td>9</td>
<td>CHF</td>
<td>Yes</td>
<td>1.5</td>
<td>5 (53)</td>
</tr>
<tr>
<td>Fleg et al (45)</td>
<td>1982</td>
<td>30</td>
<td>CHF</td>
<td>Yes</td>
<td>6</td>
<td>0 (0)</td>
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<tr>
<td>Lee et al (46)</td>
<td>1982</td>
<td>25</td>
<td>CHF</td>
<td>Yes</td>
<td>1 to 5</td>
<td>14 (53)</td>
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<tr>
<td>Griffiths et al (47)</td>
<td>1982</td>
<td>11</td>
<td>U</td>
<td>Yes</td>
<td>1.5</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Gheorghiade &amp; Beller (36)</td>
<td>1983</td>
<td>24</td>
<td>CHF</td>
<td>Yes</td>
<td>1</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*Thirteen patients with atrial fibrillation were included into the trial.
†Only patients with an S3 gallop had a clinical deterioration when digoxin was discontinued.
CHF = congestive heart failure, and U = unclear.
Digitalis and Heart Failure—Gheorghiade


