Digoxin in the Management of Cardiovascular Disorders

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“After all, in spite of opinion, prejudice or error, time will fix the real value upon this discovery.”
Sir William Withering, Birmingham, July 1, 1785

Case 1: A 45-year-old man in sinus rhythm, with an ejection fraction of 20%, normal coronaries, and normal renal function is receiving captopril 50 mg 3 times daily, carvedilol 25 mg and furosemide 40 mg twice daily, and spironolactone 25 mg daily. Despite these therapies, he continues to complain of dyspnea with minimal exertion. Oral digoxin, 0.125 mg daily, is added. After 3 weeks of maintenance therapy with digoxin, the patient feels better.

Case 2: A 70-year asymptomatic woman in sinus rhythm, with coronary artery disease and ejection fraction of 35% is receiving once a day enalapril 10 mg, metoprolol succinate 200 mg, digoxin 0.125 mg, and furosemide 20 mg. There are no signs of heart failure. Six months after digoxin discontinuation she continues to remain asymptomatic.

Historical Perspectives
As far back as the ancient Egyptians, cultures were known to have used medicinal plants containing cardiac glycosides. It was not until 1542 that the German scholar Fuchsius coined the now common term digitalis for the foxglove plant. Since 1785, when Sir William Withering published his textbook on the “account of the foxglove,” physicians have used digitalis preparations to treat edematous states, irregular heartbeats, and chronic heart failure (HF). According to Withering, digitalis was believed to slow heart rate in patients with irregular pulse and result in diuresis.

Mechanism of Action
Digoxin’s primary mechanism of action is the ability to inhibit membrane-bound alpha subunits of sodium-potassium ATPase (sodium pump), mainly but not exclusively located in the human myocardium. This inhibition promotes sodium-calcium exchange, which increases the intracellular calcium concentration that is available to the contractile proteins, resulting in an increase in the force of myocardial contraction. In the human myocardium, there is no evidence of up-regulation of the sodium pump during chronic digoxin therapy. The inhibition of the sodium pump may also improve baroreceptor sensitivity in HF and may explain some of the neurohormonal effects of digoxin. Digoxin also has important parasympathetic effects, particularly on the atrioventricular node.

Hemodynamic Effects
Digitalis administration does not alter cardiac output in normal subjects, although it does cause significant increase in contractility. This lack of effect on cardiac output is likely due to an increase in systemic vascular resistance produced by digitalis that prevents the increase in contractility from translating into increased cardiac output.

In patients with reduced systolic function and abnormal central hemodynamics who are in sinus rhythm, digoxin improves left ventricular ejection fraction (LVEF) and reduces pulmonary capillary wedge pressure while increasing cardiac output both at rest and during exercise. In HF, however, when hemodynamics are normalized first with diuretics and vasodilators, no further improvement in pulmonary capillary wedge pressure or cardiac output is achieved after the acute administration of digoxin. The improvement in hemodynamics is sustained during chronic therapy.
Neurohormonal Effects
The beneficial effects of digoxin on HF may be related in part to its modulating effects on neurohormonal abnormalities:

1. Baroreceptor function: In low-output HF models, there is attenuation of carotid sinus baroreceptor discharge sensitivity. Administration of digoxin produces improvement in baroreceptor function that results in decreased activation of the sympathetic nervous system.

2. Vagomimetic effect: Digoxin at therapeutic doses increases vagal tone (ie, decreases sinoatrial and atrioventricular conduction).

3. Sympathoinhibitory effects: Digoxin has a direct sympathoinhibitory effect that does not appear to be related to an increase in the cardiac output produced by the drug. Although dobutamine and digoxin cause a similar increase in cardiac output in HF, only the latter decreases sympathetic nerve discharge.


5. Dose related effects on neurohormones: A low dose of digoxin that has no effect on cardiac contractility or hemodynamics decreases cardiac norepinephrine spillover in severe HF. Increasing the dose within therapeutic range continues to improve the hemodynamics without further improvement of the neurohormonal profile.

6. Antifibrotic effects: Patients with HF often have chronically high levels of aldosterone. Aldosterone stimulation of the sodium pump may lead to perivascular fibrosis that experimentally may be prevented by digoxin administration.

Electrophysiological Effects
Therapeutic doses of digoxin have a predominantly parasympathomimetic action on atrial myocardium, slowing conduction, and prolonging atrioventricular node refractory period. There are practically no electrophysiological effects on the Purkinje system. Although digoxin intoxication may produce lethal arrhythmias, therapeutic doses do not appear to increase arrhythmias in the absence of ischemia.

Pharmacokinetics
Sixty to 80 percent of digoxin is absorbed from the tablets and over 90% from the capsules in 1 to 3 hours. This is followed by a 6- to 8-hour tissue distribution phase. In some patients, oral digoxin is partially inactivated by colonic bacteria; as a result, certain antibiotics may increase digoxin absorption. Only 16% of the absorbed digoxin is metabolized, whereas the rest is excreted unchanged in the urine. The half-life of digoxin is 36 to 48 hours in patients with normal renal function and 3.5 to 5 days in anuric patients. Digoxin is not removed by exchange transfusions or peritoneal dialysis, or during cardiopulmonary bypass. In patients with normal renal function, an oral daily maintenance dose without a loading dose results in a steady-state blood concentration in approximately 7 days.

Clinical Effects
Approximately 1.7 million patients in the United States are currently receiving digoxin for HF and/or atrial fibrillation. It is not clear whether the beneficial effects of digoxin seen in patients with HF and reduced systolic function are related to its hemodynamic effects, neurohormonal effects, or both. The rapidity by which patients deteriorate when digoxin is discontinued suggests, however, that its hemodynamic effects are important.

Heart Failure With Systolic Dysfunction
Withdrawal Trials Assessing Clinical Effects
In several studies, digoxin withdrawal in patients with systolic dysfunction and sinus rhythm was associated with a decrease in LVEF and exercise tolerance and an increase in heart rate, diastolic pressure, body weight and/or cardiac size on chest x-ray (Table 1).

Effects on Mortality
The Digitals Investigation Group (DIG) was a large simple trial that assessed all-cause mortality in patients in sinus rhythm with HF and decreased systolic function while receiving diuretics and angiotensin-converting enzyme inhibitors. Approximately 50% of patients were not taking digoxin before randomization. In this trial, although digoxin had neutral effects on mortality, hospitalizations related to worsening HF were significantly reduced. Patients with severe symptoms, cardiomegaly, or very low LVEF on chest x-ray appeared to derive a significant benefit from digoxin, reflected by a decrease in total mortality and total hospitalizations (Table 2).

Diastolic Heart Failure
It is estimated that between 30% and 40% of patients with HF have relatively preserved systolic function or diastolic HF. In the DIG ancillary study, which enrolled nearly 1000 patients with diastolic HF, digoxin therapy was associated with a reduction in worsening HF but not mortality.

Atrial Fibrillation
Rate Control
Because it can be taken once daily, is well tolerated, is inexpensive, and allows for measurement of plasma concentration if intoxication is suspected, digoxin remains an important drug for rate control in atrial fibrillation. However, in patients with increased sympathetic activity (eg, during exercise, decompensated HF, or infusion of dopamine or dobutamine), digoxin alone is unlikely to adequately control ventricular response unless large toxic doses are used. Although beta-blockers alone or non-dihydropyridine calcium channel blockers alone have been advocated to control rate, usually the doses used had been high and caused significant side effects. The most likely combination to effectively control ventricular response in patients with atrial fibrillation and HF due to systolic dysfunction is a combination of digoxin and beta-blockers.
Rhythm Control
Digoxin does not appear to restore sinus rhythm in patients with atrial fibrillation without HF. In patients with paroxysmal atrial fibrillation, digoxin may reduce the frequency of symptomatic atrial fibrillation. Digoxin should not be used in multifocal atrial tachycardia.

Digoxin Dose/
Serum Concentration
Low dose digoxin, resulting in a serum concentration (SDC) less than 1 ng/mL, has beneficial hemodynamic, neurohormonal, and clinical effects. retrospective analysis of the DIG trial suggests that digoxin has a bidirectional effect, with a possible decrease in mortality when SDC is 0.5 to 0.9 ng/mL and an increase in mortality when SDC is above 1 ng/mL. Additional data from the DIG trial suggest that in patients with normal renal function who are not receiving medications that tend to increase SDC, a dose of 0.125 mg daily will result in SDC of approximately 0.8 ng/mL. Determination of SDC is not routinely necessary because it is predictable based on dose used. Only the post-distribution phase (12 to 24 hours after the dose) is useful to evaluate whether the dose of digoxin is acceptable.

Drug Interactions
Drugs concomitantly used with digoxin may affect its absorption, clearance, volume of distribution, or potentiation of its effects. Quinidine, verapamil, and amiodarone, among others, may significantly increase the SDC, and the digoxin dose should be reduced accordingly. Non-potassium sparing diuretics could be a major contributing factor to digoxin toxicity by causing hypokalemia.

Digoxin Intoxication
Although digoxin intoxication used to be very common and associated with a high mortality, in recent years its prevalence has substantially decreased to less than 1%. Digoxin intoxication can cause arrhythmias and gastrointestinal and/or central nervous system abnormalities. The intoxication is not only dose-dependent but is also related to concurrent medications (non-potassium sparing diuretics) or conditions (renal insufficiency, ischemia, cardiac amyloidosis). A distinction should be made between a digoxin effect (sagging of the ST segments), digoxin excess (second degree atrioventricular block), digoxin intoxication (ventricular arrhythmias), and digoxin overdose (ventricular arrhythmias and severe hyperkalemia). In patients with intoxication and life-threatening arrhythmias or ingestion of a very large dose of digoxin resulting in a very high SDC, purified anti-digoxin FAB fragments from digoxin-specific antisera is usually administered with excellent results.

**TABLE 1. Double-Blind, Randomized, Placebo-Controlled Studies of Digoxin in Patients With Heart Failure**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Design</th>
<th>Duration, wk</th>
<th>No. Patients</th>
<th>NYHA Functional Class</th>
<th>EF, %</th>
<th>SDC, ng/mL</th>
<th>Concomitant Therapy, %</th>
<th>Worsening of HF, %</th>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobbs et al, 1977</td>
<td>CO</td>
<td>6</td>
<td>46</td>
<td>NA</td>
<td>NA</td>
<td>1.3</td>
<td>60</td>
<td>0</td>
<td>NA</td>
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<tr>
<td>Lee et al, 1982</td>
<td>CO</td>
<td>9</td>
<td>35</td>
<td>II to III</td>
<td>29</td>
<td>1.15</td>
<td>88</td>
<td>24</td>
<td>NA</td>
</tr>
<tr>
<td>Fleg et al, 1982</td>
<td>CO</td>
<td>12</td>
<td>40</td>
<td>II to III</td>
<td>23 (FS)</td>
<td>1.4</td>
<td>77</td>
<td>17</td>
<td>NS</td>
</tr>
<tr>
<td>Taggart et al, 1983</td>
<td>CO</td>
<td>12</td>
<td>22</td>
<td>I to II</td>
<td>NA</td>
<td>0.8</td>
<td>96</td>
<td>36</td>
<td>NA</td>
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<tr>
<td>Captopril-Digoxin, 1988</td>
<td>PA</td>
<td>24</td>
<td>196</td>
<td>II to III</td>
<td>25</td>
<td>0.7</td>
<td>86</td>
<td>0</td>
<td>No</td>
</tr>
<tr>
<td>Guyatt et al, 1988</td>
<td>CO</td>
<td>7</td>
<td>28</td>
<td>II to III</td>
<td>19 (FS)</td>
<td>1.37</td>
<td>90</td>
<td>55</td>
<td>No*</td>
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<tr>
<td>German/Austrian Xamoterol, 1988</td>
<td>PA</td>
<td>12</td>
<td>213</td>
<td>I to III</td>
<td>NA</td>
<td>0.9</td>
<td>25</td>
<td>10</td>
<td>No</td>
</tr>
<tr>
<td>Haerer et al, 1988</td>
<td>PA</td>
<td>3</td>
<td>28</td>
<td>I to III</td>
<td>25 (FS)</td>
<td>1.8</td>
<td>0</td>
<td>0</td>
<td>Yes*</td>
</tr>
<tr>
<td>Milrinone Multicenter Trial, 1989</td>
<td>PA</td>
<td>12</td>
<td>111</td>
<td>II to III</td>
<td>25</td>
<td>1.2</td>
<td>100</td>
<td>48</td>
<td>Yes</td>
</tr>
<tr>
<td>Pugh et al, 1989</td>
<td>CO</td>
<td>8</td>
<td>44</td>
<td>NA</td>
<td>27 (FS)</td>
<td>1.4</td>
<td>75</td>
<td>9</td>
<td>NA</td>
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<tr>
<td>Fleg et al, 1991</td>
<td>CO</td>
<td>4</td>
<td>10</td>
<td>II to III</td>
<td>33</td>
<td>1.4</td>
<td>100</td>
<td>50</td>
<td>NS</td>
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<tr>
<td>Drozler et al, 1992</td>
<td>PA</td>
<td>104</td>
<td>133</td>
<td>II to III</td>
<td>50</td>
<td>NA</td>
<td>9</td>
<td>8</td>
<td>Yes†</td>
</tr>
<tr>
<td>DMT, 1993</td>
<td>PA</td>
<td>26</td>
<td>108</td>
<td>II to III</td>
<td>28</td>
<td>0.94</td>
<td>0</td>
<td>56</td>
<td>Yes*</td>
</tr>
<tr>
<td>PROVED, 1993</td>
<td>PA</td>
<td>12</td>
<td>88</td>
<td>II to III</td>
<td>27</td>
<td>1.2</td>
<td>100</td>
<td>0</td>
<td>Yes*</td>
</tr>
<tr>
<td>RADIANCE, 1993</td>
<td>PA</td>
<td>12</td>
<td>178</td>
<td>II to III</td>
<td>26</td>
<td>1.2</td>
<td>100</td>
<td>100§</td>
<td>Yes*</td>
</tr>
<tr>
<td>DIG Trial, 1997</td>
<td>PA</td>
<td>148</td>
<td>6900</td>
<td>I to IV</td>
<td>29</td>
<td>0.9</td>
<td>82</td>
<td>95§</td>
<td>NA</td>
</tr>
</tbody>
</table>

CO indicates cross-over; D, diuretics; Dig, digoxin; EF, ejection fraction; ExT, significant increase in exercise time; FS, fractional shortening on echocardiogram; HF, heart failure; NA, not available; NYHA, New York Heart Association; P, placebo; PA, parallel; SDC, serum digoxin concentration; DMT, Dutch Ibopamine Multicenter Trial; PROVED, the Prospective Randomized study Of Ventricular failure and the Efficacy of Digoxin; RADIANCE, Randomized Assessment of the effect of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme study; and V, vasodilator.

*P<0.05.
†Trend.
§Hospitalization for heart failure.
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Special Considerations in the Use of Digoxin

Women
More than 50% of patients with HF are women. Retrospective analysis of the DIG trial suggested that digoxin might increase mortality in women. One concern about this conclusion is that SDC was not taken into account in this investigation, particularly when detailed analysis by the same authors suggested a relationship between SDC and outcomes in men. For now it is prudent to administer low doses of digoxin only in women with HF with very low LVEF and symptoms that occur with minimal exertion or at rest despite standard therapy.

Elderly
Because the elderly have a lower lean body mass and decreased renal function, digoxin should be used with caution. Digoxin is not likely to benefit elderly patients with diastolic HF unless they have atrial fibrillation with a rapid ventricular response.

Coronary Artery Disease
Myocardial ischemia in itself may cause inhibition of sodium pump, rendering myocardial tissue more sensitive to the arrhythmogenic effects of digitalis, even at lower SDC. Digoxin should be used in very low doses or not used at all in patients with acute coronary syndromes or significant ischemia.

Advanced Heart Failure
Digoxin may be particularly beneficial in patients with a LVEF less than 25%, symptoms with minimal exertion or at rest, and/or cardiomegaly on chest x-ray.

Acute Heart Failure Syndrome
In patients hospitalized for HF and systolic dysfunction, oral or intravenous administration of digoxin will increase the cardiac output, reduce pulmonary capillary wedge pressure and heart rate, and improve the neurohormonal profile. These beneficial hemodynamic effects have not been correlated with symptoms. Rapid intravenous administration of digoxin as a bolus may result in worsening HF through an early predominant vasoconstrictor effect.

Isolated Right-Sided Heart Failure
Digoxin increases cardiac output and decreases norepinephrine concentration in patients with right ventricular failure due to cor pulmonale. There are no clinical data supporting the use of digoxin for isolated right-sided failure.

Digoxin in the Multidrug Approach of Heart Failure

Diuretics
Because digoxin affects potassium homeostasis, combination therapy with non-potassium sparing diuretics may induce serious arrhythmias. In these patients, high normal concentration of potassium and magnesium should be maintained. The arrhythmogenic effects of digoxin may be lessened by potassium sparing diuretics.

Beta-Blockers
Although chronic beta-blocker therapy is highly beneficial in HF, during its initiation, hemodynamic deterioration may occur, particularly in patients with very severe HF. Because digoxin is known to rapidly improve hemodynamics in HF, theoretically it may prevent this transient deterioration. The effect may be particularly important in hospitalized patients with HF who already have very abnormal hemodynamics. Beta-blocker use may also increase the safety of digoxin therapy, because experimentally they can abolish the digoxin-induced life-threatening arrhythmias in ischemic HF.

Precautions in Using Digoxin
Digoxin should not be used in patients with sinoatrial or second/third degree atrioventricular block unless a functioning pacemaker is present.

Table 2: Subgroup Analyses of Mortality and Hospitalization During the First 2 Years After Randomization in the Digitalis Investigation Trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients</th>
<th>Placebo</th>
<th>Digoxin</th>
<th>RR (95% CI)</th>
<th>Placebo</th>
<th>Digoxin</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (EF ≤0.45)</td>
<td>6801</td>
<td>604</td>
<td>593</td>
<td>0.94 (0.88 to 1.00)</td>
<td>294</td>
<td>217</td>
<td>0.69 (0.63 to 0.76)</td>
</tr>
<tr>
<td>NYHA FC I/II</td>
<td>4571</td>
<td>548</td>
<td>541</td>
<td>0.96 (0.89 to 1.04)</td>
<td>242</td>
<td>178</td>
<td>0.70 (0.62 to 0.80)</td>
</tr>
<tr>
<td>EF 0.25 to 0.45</td>
<td>4543</td>
<td>568</td>
<td>571</td>
<td>0.99 (0.91 to 1.07)</td>
<td>244</td>
<td>190</td>
<td>0.74 (0.66 to 0.84)</td>
</tr>
<tr>
<td>Cardiothoracic ratio on chest x-ray ≤0.55</td>
<td>4455</td>
<td>561</td>
<td>569</td>
<td>0.98 (0.91 to 1.06)</td>
<td>239</td>
<td>180</td>
<td>0.71 (0.63 to 0.81)</td>
</tr>
<tr>
<td>NYHA FC III/IV</td>
<td>2224</td>
<td>719</td>
<td>696</td>
<td>0.88 (0.80 to 0.97)</td>
<td>402</td>
<td>295</td>
<td>0.65 (0.57 to 0.75)</td>
</tr>
<tr>
<td>EF&lt;0.25</td>
<td>2258</td>
<td>677</td>
<td>637</td>
<td>0.84 (0.76 to 0.93)</td>
<td>394</td>
<td>270</td>
<td>0.61 (0.53 to 0.71)</td>
</tr>
<tr>
<td>Cardiothoracic ratio on chest x-ray&gt;0.55</td>
<td>2346</td>
<td>687</td>
<td>650</td>
<td>0.55 (0.77 to 0.94)</td>
<td>398</td>
<td>287</td>
<td>0.65 (0.57 to 0.75)</td>
</tr>
<tr>
<td>EF≥0.45†</td>
<td>987</td>
<td>571</td>
<td>585</td>
<td>1.04 (0.88 to 1.23)</td>
<td>179</td>
<td>136</td>
<td>0.72 (0.53 to 0.99)</td>
</tr>
</tbody>
</table>

RR indicates relative risk; CI, confidence interval; EF, ejection fraction; and NYHA FC, New York Heart Association Functional Class.

*No. of patients with an event during the first 2 years per 1000 randomized patients.
†DIG Ancillary Study.
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should also not be used in Wolff-Parkinson-White syndrome, hypertrophic or restrictive cardiomyopathy, and amyloid heart disease. It should be used with caution in patients with impaired renal function, electrolyte disorders, thyroid disorders, and acute coronary syndromes. It is preferable to discontinue digoxin a few days before electrical cardioversion. If cardioversion is performed in patients receiving digoxin, potassium levels should be corrected, and the lowest energy possible should be used.

**Indications for Digoxin Therapy**

Digoxin is indicated in patients with HF and impaired systolic function who are in sinus rhythm and continue to have signs and symptoms despite standard therapy that includes angiotensin-converting enzyme inhibitors and beta-blockers. Digoxin may be particularly useful in patients with severe symptoms, LVEF less than 25%, or cardiomegaly on chest x-ray. In patients with diastolic HF, digoxin should be used for atrial fibrillation with a rapid ventricular response and/or severe symptoms not responding after optimization of all other therapies. Digoxin is indicated in patients with atrial fibrillation, with or without HF, and a rapid ventricular response. Irrespective of the indication, a low dose of 0.125 mg should be used. Digoxin should be avoided or used with extreme caution in the very elderly or in patients with severe conduction abnormalities, acute coronary syndromes, or renal failure.

**References**

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