Digitalis Therapy for Patients in Clinical Heart Failure

Shahbudin H. Rahimtoola, MB, FRCP, DSc (Hon)

The most commonly used preparation of digitalis is digoxin, which is obtained from the leaves of Digitalis lanata, a common flowering plant called “foxglove.” The words digitalis and digoxin in this article are used interchangeably. An exhaustive review published in 1996 cited a large number of references and had detailed data and descriptions of a large number of studies and all early trials. The present article summarizes those data but focuses on and emphasizes data collected since that time.

Actions of Cardiac Glycosides

These have been described in detail previously and are briefly summarized.

Inotropic Effects

The inotropic effects have been documented in the isolated papillary muscles and in the normal hearts of animals and humans. The inotropic action occurs in both ventricles and in both atria. In the normal heart and in those with coronary artery disease and normal left ventricular (LV) systolic function, with digitalis the LV function curve is moved upward and to the left.1 As a result, LV end-diastolic pressure and LV end-diastolic and end-systolic volumes are reduced, and there is an increase of LV ejection fraction (LVEF).1

Patients With Heart Failure

In patients with heart failure (HF), digoxin slows the ventricular rate (1) in sinus rhythm because of an improvement in HF and withdrawal of sympathetic stimulation and (2) in atrial fibrillation by increasing parasympathetic tone. The combination of digoxin and carvedilol is superior to digoxin or carvedilol alone.2

Peripheral Vessels

In normal subjects given intravenous ouabain, there is arterial and venous vasoconstriction.3 The vasoconstriction is obviated by administering digoxin slowly over a period of 15 to 20 minutes; moreover, the vasoconstriction lasts up to 30 minutes. The seminal study of Mason and Braunwald showed that in HF, the effects are different. Digitalis produces an increase of blood flow, a decrease of vascular resistance, venodilation, and a decrease of central venous pressure and heart rate (Figure 1). The vasodilation is the result of an increase in cardiac output and direct baroreflex-mediated withdrawal of sympathetic vasoconstriction. The reduction of systemic vascular resistance in patients in HF has been repeatedly confirmed.1

Coronary Circulation

The effect of intravenous digoxin on the coronary vasculature is similar to those described above. The vasoconstriction can produce transient myocardial ischemia in those with severely obstructed coronary artery disease. These effects are prevented by administering intravenous digoxin slowly over a period of 15 minutes.1

Baroreflexes

Digitalis normalizes the blunted baroreflex mechanisms present in HF.4 Digitalis produces a rapid and profound alteration of sympathetic nerve activity before the hemodynamic effects are observed; that is, there may be dissociation between the neuroendocrine and hemodynamic effects.4

Neurohormonal

In HF, digitalis therapy has been shown to reduce plasma norepinephrine levels, serum aldosterone, and plasma renin activity, which has been repeatedly documented.5

Diuretic

Digoxin induces diuresis in patients with HF who have fluid retention. The mechanism(s) are multiple: (1) vasodilation and increased CO improves renal hemodynamics; (2) inhibition of tubular reabsorption of sodium, of renal Na+/K+-ATPase, and of concentrating and diluting ability; and (3) increased secretion of atrial natriuretic peptide.

Summary

In patients in HF, the multiple actions of digitalis are

- Positive inotropic
- Slowing of rapid ventricular rate
- Vasodilation
- Increasing baroreceptor sensitivity
- Reducing plasma neurohormones
- Increasing vagal tone
- Diuresis

Beneficial Clinical Effects

There have been 16 small, randomized trials and 8 nonrandomized studies that were reviewed previously. In
brief, these have documented symptomatic improvement, improved HF score, increased exercise capacity and VO₂, improved hemodynamics at rest and on exercise, decreased heart rate, and other beneficial effects (Table 1). In each study, only a few parameters were measured. LV function from one study (Figure 2) shows that at rest and on exercise, when digoxin is added to diuretics or to diuretics and ACE inhibitors (ACE-I), the LV is functioning at a lower left atrial pressure but has an increased cardiac output, which is the hemodynamic explanation for the improvement in symptoms, exercise capacity, and reduction of worsening HF with digoxin. Data from 12 randomized trials had shown that the incidence of worsening HF in the nondigitalis group was 24% and in the digitalis group was 5%.¹

**PROVED and RADIANCE Trials**

Two of these small trials are described in further detail. Patients were in New York Heart Association functional classes II and III and had LV EF < 0.35. Both of these were digoxin discontinuation trials. The Prospective Randomized study Of Ventricular failure and the Efficacy of Digoxin (PROVED) trial²¹ was a comparison of digoxin and diuretics versus diuretics; the Randomized Assessment of Digoxin on Inhibitors of the ANgiotensin Converting Enzyme (RADIANCE) trial²² was a comparison of digoxin, diuretics, and ACE-I versus diuretics plus an ACE-I. In the PROVED trial, the digoxin group had a lower incidence of worsening HF and of hospitalization for HF, lower BUN and creatinine levels, a higher LV EF, and better exercise capacity, which was documented objectively. In the RADIANCE trial, the digoxin group had a lower incidence of worsening HF and a better LV EF, quality of life, and exercise capacity, which was documented objectively.

**Further Analysis From the PROVED and RADIANCE Trials**

Further analysis from the PROVED and RADIANCE trials have shown the following important additional information:

<table>
<thead>
<tr>
<th>Table 1. Beneficial Clinical Effects of Digitalis Therapy for Heart Failure</th>
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<tbody>
<tr>
<td><strong>Clinical improvement</strong>,⁵,⁷,¹²,¹³,¹⁵–¹⁷,²¹,²²,²⁵</td>
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<tr>
<td><strong>Symptoms</strong></td>
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<tr>
<td><strong>NYHA functional class</strong></td>
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<tr>
<td><strong>HF score</strong></td>
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<tr>
<td><strong>Increases exercise capacity</strong></td>
</tr>
<tr>
<td><strong>Exercise time</strong>,¹³,¹⁴,¹⁶,¹⁷</td>
</tr>
<tr>
<td><strong>Total body O₂ consumption on exercise</strong></td>
</tr>
<tr>
<td><strong>Decreases frequency of</strong></td>
</tr>
<tr>
<td>**Clinical decompensation (worsening of heart failure)**³,⁵–¹⁷,²¹,²²,²⁵</td>
</tr>
<tr>
<td><strong>Hospitalization for HF</strong>,²¹,²²,²⁵</td>
</tr>
<tr>
<td><strong>Deaths attributable to worsening HF</strong>,²⁵</td>
</tr>
<tr>
<td><strong>Reduces costs of treatment of HF</strong>,²³</td>
</tr>
<tr>
<td><strong>Increases LV EF</strong>,¹²,¹³,¹⁷,²⁰–²²</td>
</tr>
<tr>
<td><strong>Reduction of LV dimensions</strong>,¹³,¹⁹</td>
</tr>
<tr>
<td><strong>Improves hemodynamics at rest and on exercise</strong></td>
</tr>
<tr>
<td><strong>Reduces LV filling pressure and mean pulmonary artery wedge pressure</strong></td>
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<tr>
<td><strong>Increases CO</strong></td>
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<tr>
<td><strong>Reduces ventricular rate</strong></td>
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<tr>
<td><strong>Reduces elevated neurohormones</strong>,²⁴</td>
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<tr>
<td><strong>Improves renal function</strong></td>
</tr>
<tr>
<td><strong>Reduction of BUN and creatinine</strong>,²¹</td>
</tr>
<tr>
<td><strong>Increased creatinine clearance</strong></td>
</tr>
</tbody>
</table>

References are provided only for randomized trials. For detailed review of each trial that is cited and for nonrandomized studies, please see Reference 1.
Use of digoxin therapy in patients with stable HF would result in net annual savings of $406 million, with a 90% range of probability of $106 to $822 million.23

The efficacy of 3 levels of serum digoxin concentration (SDC) of 0.5 to 0.9 mg/mL, >0.9 to ≤1.2 ng/mL, and >1.2 ng/mL with regard to LVEF and patient outcomes were evaluated.24 LVEF fell in patients assigned not to receive digoxin and increased in those who received digoxin (P<0.0001); treadmill times were reduced in those not receiving digoxin and were unchanged in those receiving digoxin (P<0.0001). Multivariate Cox analysis demonstrated that the risk of worsening HF was significantly less for all 3 subgroups of patients who continued to receive digoxin after adjustment for LVEF, cardiothoracic ratio, age, HF score, and ACE-I use (Figure 3). There was no relation between SDC levels and changes in LVEF, treadmill times, and development of worsening HF. The incidence of worsening HF in the placebo group was 30% and in the 3 digoxin subgroups was 6%, 9%, and 12%, respectively (P<0.02 for no digoxin versus the digoxin subgroups).

The Digitalis Investigation Group Trial
The Digitalis Investigation Group (DIG) trial is the largest trial of digitalis.25 It had two parts: the main trial and the ancillary trial.

Main Trial
In the main trial, 6800 patients with LVEF ≤0.45 were randomly assigned to digoxin or placebo: The placebo group received diuretics (82%) and ACE-I (95%) and the digoxin group received digoxin, diuretics (81%), and ACE-I (94%). The main findings were that digoxin

- Had no effect on total mortality rates
- Reduced incidence of
  - Death or hospitalization caused by worsening HF [P<0.001 (Figure 4); risk ratio was 0.75 in the whole group and was ≤0.80 in all subgroups (Table 2)]
  - Hospitalization for worsening HF (P<0.001)
  - Death caused by worsening HF (P=0.06)
- Benefits were incremental to use of diuretic and ACE-I

Ancillary Trial
In the ancillary trial, 988 patients with LVEF >0.45 were randomly assigned to digoxin or placebo. It showed

- Death or hospitalization for worsening HF was lower in patients assigned to digoxin (risk ratio, 0.82; 95% CI, 0.63 to 1.07) and “were consistent with the findings of the main trial” 25

Subgroup Analysis
A post hoc subgroup analysis 26 showed at the end of 5 years that women had a higher mortality rate than men (33.1% versus 28.9%; absolute difference, 4.2%; 95% CI, −0.5 to 8.8).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF 0.25−0.45</td>
<td>0.80 (0.72 to 0.89)</td>
</tr>
<tr>
<td>&lt;0.25</td>
<td>0.68 (0.60 to 0.77)</td>
</tr>
<tr>
<td>Previous use of digoxin</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.74 (0.66 to 0.83)</td>
</tr>
<tr>
<td>No</td>
<td>0.77 (0.68 to 0.86)</td>
</tr>
<tr>
<td>Cause of HF</td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>0.79 (0.72 to 0.88)</td>
</tr>
<tr>
<td>Nonischemic</td>
<td>0.67 (0.58 to 0.77)</td>
</tr>
<tr>
<td>Cardiothoracic ratio</td>
<td></td>
</tr>
<tr>
<td>≤0.55</td>
<td>0.79 (0.71 to 0.88)</td>
</tr>
<tr>
<td>&gt;0.55</td>
<td>0.69 (0.61 to 0.78)</td>
</tr>
<tr>
<td>NYHA functional class</td>
<td></td>
</tr>
<tr>
<td>I or II</td>
<td>0.78 (0.70 to 0.87)</td>
</tr>
<tr>
<td>III or IV</td>
<td>0.70 (0.61 to 0.79)</td>
</tr>
<tr>
<td>Overall study population</td>
<td>0.75 (0.69 to 0.82)</td>
</tr>
</tbody>
</table>

Reproduced with permission from Reference 25.
Digitalis Toxicity
In the DIG trial, “suspected digoxin toxicity” was diagnosed in 11.9% in the digoxin-treated group and 7.9% in the placebo groups. Hospitalization for “suspected digoxin toxicity” in the two groups was 2.0% and 0.9%, respectively. Serum digoxin concentration in the digoxin group was >2.0 ng/mL in 2% and was 1.5 to 2.0 ng/mL in 5%. SDC ≥2.0 ng/mL was present in 2.3% of men and 3.4% of women 1 month after random assignment. The incidence of digoxin-induced arrhythmia at a level of 1.7 ng/mL is 10% and at 2.5 ng/mL is 50%, which increases with increasing blood levels. Thus, digoxin toxicity may have accounted for excess deaths in women and for deaths ascribed as not caused by HF in the DIG main trial.

HF With Normal LVEF
In patients with HF and normal LVEF (≥0.50), there are virtually no good studies documenting that digitalis therapy is not of value. On the other hand, there are data to show that

- In people with normal heart and in those with coronary artery disease but with normal LVEF, digitalis
- Increases myocardial contractility
- Moves LV function curve upward and to the left
- Reduces LV end-diastolic and end-systolic volumes
- The Ancillary part of the DIG trial showed that in those with HF and LVEF >0.45, the incidence of death or hospitalization for worsening HF was reduced and was consistent with the findings in the main trial.
- Digitalis attenuates sympathetic nerve activity, and this precedes the hemodynamic effects. In other words, there is dissociation between the neuroendocrine and hemodynamic effects. Thus, it is possible that even if the beneficial hemodynamic effects are attenuated or are absent, digitalis therapy may still have some beneficial effects.

Good studies are needed in patients with HF and normal LVEF.

American College of Cardiology/American Heart Association Guidelines for Chronic Heart Failure
The American College of Cardiology/American Heart Association Guidelines for Chronic Heart Failure gives digitalis therapy for clinical HF a class 1 grading (that is, conditions for which there is evidence and/or general agreement that a given procedure/therapy is useful and effective) and gives level of evidence an A classification (that is, the data were derived from multiple randomized clinical trials).

Recommendation
Digitalis was recommended for the treatment of symptoms of HF unless contraindicated. In other words, all patients with clinical HF (that is, those in NYHA functional classes II-IV) and LV systolic dysfunction should receive digitalis, unless contraindicated.

Advantages of Digitalis Therapy in Clinical HF
- Stood test of time (in use 228 years)
- Given orally, once a day
- Easily tolerated
- Side effects infrequent
- Has multiple actions: all mild
- Has multiple beneficial clinical effects (Table 1)
- Inexpensive
- Reduces costs of treating heart failure

β-Blockers, ACE-I, Angiotensin Receptor Blockers, Aldosterone Blockers
In randomized trials of β-adrenergic receptor blockers (β-blockers), the patients in the β-blocker group also received digitalis (53%, 64%, 67%), diuretics (98%, 90% and 99%), ACE-I (96%, 96%), or ACE-I/angiotensin receptor blockers (ARB) (96%). In randomized trials of ACE-I, patients in the ACE-I group also received digitalis (92%, 66%, “optimal” dose) and diuretics (100%, 95%, “optimal” dose).

A meta-analysis of randomized trials of ARBs in heart failure showed that ARBs were not superior to ACE-I with regard to reducing all-cause mortality rates or hospitalization of HF. A more recent trial also showed that ARBs were not superior to ACE-I in the treatment of heart failure or LV dysfunction after myocardial infarction. In the Randomized Aldactone (spironolactone) Evaluation Study for congestive heart failure (RALES) trial, patients in the spironolactone group received digoxin (75%), diuretics (100%), ACE-I/ARB (95%), and β-blockers (11%). Moreover, in the subgroup analysis of the RALES trial, patients who were in the spironolactone group the benefit was not statistically significant in the patients who did not receive digoxin or ACE-I.

In a small diuretics withdrawal trial, patients who were “stable” only with the use of diuretics were randomly assigned to diuretics versus ACE-I. In the ACE-I group, 28.6% of patients had deteriorated within 8 to 33 days, with occurrence of pulmonary edema and “increasing breathlessness.” Thus, it is scientifically and clinically correct that

- Digitalis trials were performed before trials of β-blockers and ARBs
- ACE-I have been shown to improve survival when combined with diuretics and digitalis
- β-Blockers have been shown to improve survival when combined with diuretics, digitalis, and ACE-I
- Spironolactone has been shown to improve survival when combined with diuretics, digitalis, and ACE-I. The beneficial effect on survival with spironolactone is not known if patients are already being treated with digitalis, diuretics, ACE-I, and β-blockers.

First-Line Pharmacological Therapy for Clinical HF
Digitalis is part of the first-line therapy for patients with clinical HF and LV systolic dysfunction. It should be combined with diuretics and ACE-I. β-Blockers (bisoprolol, metoprolol CR/XL, and carvedilol) are to be used in “stable patients.”
Suggestions for Use of Digoxin in HF

- Intravenous digoxin is rarely needed in routine clinical practice. Intravenous digoxin, if necessary, should be given slowly over a period of 20 to 30 minutes.
- Ideal SDC is 0.7 to 1.1 ng/mL and almost never exceeds 1.3 ng/mL.
- In most patients, one can start with oral digoxin 0.25 mg OD and estimate SDC at end of 5 days.
- Digoxin is eliminated primarily through the kidney. In older patients and those with known or suspected renal dysfunction, estimate creatinine clearance rapidly by using the Crockroft and Gault96 formula:

\[
\text{Creatinine clearance (CL}_{cr}) = \left(\frac{[140-\text{age}]}{\text{weight in kg}}\right) \times \frac{72}{[\text{serum creatinine in (mg/L)}]}
\]

- Multiply the CL_{cr} by 0.85 for women. CL_{cr} ≥90 use normal dosage; CL_{cr} 60 to 89, can start with digoxin 0.125 OD [estimate SDC at 5 days*]; CL_{cr} 30 to 59, can start with digoxin 0.125 mg every other day [estimate SDC on fourth day*]; CL_{cr} ≤29, extremely cautious with use of digoxin.

*Repeat as frequently as appropriate until levels of SDC are stable and in the acceptable range. SDC is usually estimated at least 6 hours after the last oral dose.

Acknowledgments

This article is dedicated to the memory of W. Thomas Smith, MD, and Richard Gorlin, MD, who made major contributions to our knowledge of digitals therapy and were the principal force behind the DIG trial.

References

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Circulation. 2004;109:2942-2946
doi: 10.1161/01.CIR.0000132477.32438.03
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

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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