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The Use of Digoxin in Patients With Worsening Chronic Heart Failure

Reconsidering an Old Drug to Reduce Hospital Admissions

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Digoxin is the oldest cardiac drug still in contemporary use, yet its role in the management of patients with heart failure (HF) remains controversial. A purified cardiac glycoside derived from the foxglove plant, digoxin increases ejection fraction, augments cardiac output, and reduces pulmonary capillary wedge pressure without causing deleterious increases in heart rate or decreases in blood pressure. Moreover, it is also a neurohormonal modulator at low doses. In the pivotal DIG (Digitalis Investigation Group) trial, digoxin therapy was shown to reduce all-cause and HF-specific hospitalizations but had no effect on survival. With the discovery of neurohormonal blockers capable of reducing mortality in HF with reduced ejection fraction, the results of the DIG trial were viewed as neutral, and the use of digoxin declined precipitously. Although modern drug and device-based therapies have dramatically improved the survival of ambulatory patients with HF, outcomes for patients with worsening chronic HF, defined as deteriorating signs and symptoms on standard therapy often leading to unscheduled clinic or emergency department visits or hospitalization, have largely remained unchanged over the past 2 decades. The available data suggest that a therapeutic trial of digoxin may be appropriate in patients with worsening chronic heart failure who remain symptomatic. (J Am Coll Cardiol 2014;63:1823–32) © 2014 by the American College of Cardiology Foundation

After all, in spite of opinion, prejudice, or error,
time will fix the real value upon this discovery.
—Sir William Withering,
Birmingham, United Kingdom, July 1, 1785 (1)

It was decided to proceed with the proposal for digitalization.…
There was no dyspnea on lying flat.…
The lungs were entirely clear.
—Dr. Howard G. Bruenn on treating
President Franklin D. Roosevelt (2)

Digoxin, a purified cardiac glycoside derived from the foxglove plant, is the oldest cardiac drug still in contemporary use (1). At its peak, digoxin was prescribed to an estimated 80% of patients with heart failure (HF) in the United States (3–5). However, in the context of the pivotal beta-blocker and angiotensin-converting enzyme inhibitor trials, the results of the DIG (Digitalis Investigation Group) trial (6), which showed that digoxin reduces the risk for hospitalization but not mortality, were interpreted with disappointment, and its use subsequently declined (Table 1) (7–13). As a result, although digoxin received approval from the U.S. Food and Drug Administration in 1997, the major guideline-issuing professional societies currently offer a secondary recommendation for digoxin in patients with HF with reduced ejection fraction (EF) in normal sinus rhythm experiencing persistent symptoms despite optimal medical therapy (14–16).

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Abbreviations and Acronyms

CI = confidence interval
CV = cardiovascular
EF = ejection fraction
HF = heart failure
HR = heart rate
NYHA = New York Heart Association
RR = risk ratio
SDC = serum digoxin concentration

Although the management of ambulatory patients with HF with reduced EF has been revolutionized over the past couple of decades by drug and device-based therapies with a mortality benefit (17), patients with worsening chronic HF, defined as deteriorating signs and symptoms on standard therapy often leading to unscheduled clinic or emergency department visits or hospitalizations, remain at high risk for admission or death (18,19). To confront this growing challenge, the Centers for Medicare and Medicaid Services have implemented financial disincentive for hospitals with excessive 30-day readmissions for HF. Given this financial impetus, it is an opportune time to reconsider existing therapies capable of reducing HF-related hospitalizations and readmissions (18,20). Thus, in this review we seek to critically reevaluate the available data on the role of digoxin in the contemporary management of HF and to provide a conceptual framework for future research.

Mechanism of Action

Digoxin and other cardiac glycosides function by inhibiting the membrane-bound Na^+/K^+–adenosine triphosphatase, thereby impeding the transport of sodium from the intracellular to the extracellular space (21). The resulting loss of the transmembrane sodium gradient decreases the activity of the Na^+/Ca^{2+} exchanger, disrupting Ca^{2+} homeostasis and increasing intracellular levels. In myocytes, raising the intracellular Ca^{2+} concentration, the pivotal link in excitation-contraction coupling, increases inotropy and the force generated (22–24). As a result, in patients with systolic dysfunction, digoxin improves left ventricular EF, augments cardiac output, and reduces pulmonary capillary wedge pressure without causing deleterious increases in heart rate (HR) or decreases in blood pressure (Table 2) (25–28).

Table 1 Prevalence of Digoxin Use at Admission and Discharge in Representative Hospital-Based Registries of Patients Admitted With Primary Diagnoses of HF

Registry	Admission	Discharge
ADHERE	30/19	44/21
OPTIMIZE-HF	30/17	38/19
EFHS II	27	31
EFICA	19	17
RO-AHFS	35	40
IN-HF Outcome	16	~24
ATTEND	~15	~25

Reported as overall percentages or divided into reduced/preserved EF.

ADHERE = Acute Decompensated Heart Failure National Registry; ATTEND = Acute Decompensated Heart Failure Syndromes; EF = ejection fraction; EFHS = EuroHeart Failure Survey; EFICA = Etude Française de l'Insuffisance Cardiaque Aiguë; HF = heart failure; IN-HF = Italian Registry on Heart Failure; OPTIMIZE-HF = Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure; RO-AHFS = Romanian Acute Heart Failure Syndromes.

For many years, it was thought that digoxin exerted its effects primarily in the myocardium, but it is now recognized that the physiologic properties of digoxin are a result of inhibition of Na^+/K^+–adenosine triphosphatase in cardiac and noncardiac tissues alike (29). In noncardiac tissue, digoxin acts as a neurohormonal modulator by increasing parasympathetic tone and decreasing activation of the sympathetic nervous system and renin-angiotensin-aldosterone system (27,30–32). Furthermore, in addition to its direct sympatholytic effects at low doses, digoxin indirectly decreases sympathetic outflow by improving carotid sinus baroreceptor sensitivity. Although digoxin improves the overall neurohormonal profile in patients with severe HF at low doses, it should be noted that further dose increases within the therapeutic range have no added neurohormonal benefit and may in fact be sympathomimetic (33,34).

Finally, digoxin slows firing at the sinoatrial node and prolongs conduction at the atrioventricular node but has limited electrophysiological effects on the remainder of the conduction system. Thus, digoxin has minimal proarrhythmic effects when dosed to achieve guideline-recommended serum digoxin concentrations (SDCs) (14–16). In contrast, at supratherapeutic SDCs or therapeutic SDCs with concomitant hypokalemia, atrioventricular block and escape rhythms are the most common electrocardiographic manifestations of toxicity.

Digoxin Withdrawal Trials

Before the pivotal DIG trial, numerous small to medium-sized randomized, double-blind, placebo-controlled trials provided evidence that digoxin improves hemodynamics and clinical status in ambulatory patients with HF with reduced EF receiving background therapy including diuretic agents with or without oral vasodilators (35). The most compelling evidence was derived from PROVED (Prospective Randomized Study of Ventricular Function and Efficacy of Digoxin) (36) and RADIANCE (Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme) (37) trials, which tested the hypothesis that digoxin withdrawal from background therapy would lead to clinical deterioration. Both studies enrolled stable ambulatory patients with HF with EFs ≤35% and New York Heart Association (NYHA) functional class II or III symptoms in normal sinus rhythm and randomized them

Table 2 Physiologic Effects of Digoxin Therapy

Hemodynamic	Neurohormonal	Electrophysiological
↑ LVEF	↑ Parasympathetic	SA node: slows sinus rate
↑ CO	↓ Sympathetic	AV node: prolongs conduction
↓ HR, ↔ BP	↓ RAAS	
↓ PCWP		

Modified and reprinted, with permission, from Gheorghiade et al. (4).

AV = atrioventricular; BP = blood pressure; CO = cardiac output; HR = heart rate; LVEF = left ventricular ejection fraction; PCWP = pulmonary capillary wedge pressure; RAAS = renin-angiotensin-aldosterone system; SA = sinoatrial.