

Founding Editor's Viewpoint

Off With the New and On With the Old: Rediscovering Digoxin

One of the valuable benefits of training at a world-class academic medical center is the exposure the neophyte gets to the greatest minds of the time. Watching a parade of perhaps the most distinguished cardiovascular physician-scientists ever collected in one place as a young house officer on the First (Columbia) Medical Division of Bellevue Hospital in New York City, I often felt that I was watching a blockbuster movie: the plot was compelling, the actors astonishingly and unusually gifted, and we house officers had front-row-center seats. For example, the 1956 Nobel laureates Dickinson W. Richards and Andre F. Cournand of Columbia University were familiar faces to us: I can still hear Cournand explaining, in his heavily accented English, that the electrical event in the heart preceded and produced the mechanical event of myocardial systole, a sequence he and his colleagues had established in 1947.¹ One of the authors of the paper proving that sequence was a 32-year-old woman in the second year of her fellowship training, M. Irene Ferrer, who spent her entire research career with these 2 distinguished investigators. Dr. Ferrer described for me the moment in Richards' office when he pushed a cardiac catheter across his desk toward her and said: "Here, Ren. See what you can do with this." She indeed did just that—in a series of brilliant protocols, she defined what could be accomplished with the cardiac catheter. I can see her still, clad in a lead apron and covered in sweat, as she emerged from the darkened cardiac catheterization laboratory after all-day investigations with the new instrument. In an astoundingly rich research career, she worked with the cardiac catheter to measure with unprecedented precision the normal operation of the pulmonary and systemic circulations; to describe the pathophysiology of cardiovascular disease; and in a fascinating series of papers, to chart the impact on the heart and circulation of one of the most important drugs ever used to treat cardiac patients, digoxin.

Because we interns and residents were in the thick of all of these heady, incredibly significant, and heretofore unimagined revelations about how and why the heart fails and how digoxin corrects that failure, we learned to use the drug with great accuracy and effectiveness. We adjusted the dose for each patient, following the electrical and contractile changes in the heart—detecting not only the virtually immediate improvement in function, but alert for the earliest signs of toxicity. Ferrer and her colleagues gave us a meticulously detailed protocol with guidelines for the proper use of the drug, which we then brought to the bedside of each patient we treated. We knew the perils of impaired renal function, low potassium levels, and hypothyroidism for the digitalized patient, and learned to titrate the medicine accurately in all those clinical situations (without benefit of serum levels of the drug, by the way; that was to come much later). We were all familiar with the incredibly positive therapeutic impact of the drug: patients with cor pulmonale, who had been considered incurable and were wheeled to the back of the ward to die, survived and flourished after Ferrer's studies proved that digitalization cured their right ventricular failure. Patients who needed fewer impulses from their fibrillating atria to reach their overtaxed ventricles profited from the drug's ability to produce higher levels of atrioventricular block. Digoxin was a miracle drug, and we used it liberally. It was the most important part of our therapeutic plan for patients in heart failure.

It's interesting to think that, like Ferrer, who was the first to document how this powerful drug worked, the person who discovered it and used it clinically was a woman too: the famous "old woman in Shropshire." She had treated patients in massive congestive heart failure 2 centuries earlier with the flowering foxglove plant (from which the cardiac glycosides come) that grew in her garden. William Withering² tells us how he discovered her secret in his 1785 report, *An Account of the Foxglove, and Some of Its Medical Uses*. He understood the importance of standardizing the dose of the drug and wrote:

“The more I saw of the great powers of this plant, the more it seemed necessary to bring the doses of it to the greatest possible accuracy...I expected if gathered always in one condition of the plant, viz, when it was in its flowering state, and carefully dried...the dose might be ascertained as exactly as that of any other medicine; nor have I been disappointed in this expectation.”

In 1960, 175 years after Withering’s report, Ferrer and her colleagues published their classic description of how digoxin relieved ventricular failure, using the cardiac catheter in living patients.³ In the clear, concise language that illuminated all her written work and her teaching, she described the increased cardiac output, the decrease in right ventricular diastolic pressure, and the lowered heart rate a single intravenous dose of digoxin produced. Two years later, all of her house staff were using digoxin on the Bellevue Hospital wards, with spectacular therapeutic results.

But over the years, in part because our understanding expanded of how complex the pathophysiology of heart failure actually is and, *pari passu*, other modalities to treat heart failure evolved,⁴ criticism of digoxin began to enter the literature. Mahdyoon et al⁵ wrote:

“Digitalis intoxication is thought to be the most prevalent adverse drug reaction encountered in clinical practice. Several studies in the 1960s and 1970s reported an incidence of digitalis intoxication ranging from 6% to 23% and a mortality rate as high as 41%.”

In fact, their study of 241 patients who had received a diagnosis of digitalis intoxication admitted over an 8-year period to a major urban hospital found that only 20% of these patients had been correctly diagnosed: the majority did not meet the criteria for digitalis intoxication. Moreover, the mortality rate in the definitely intoxicated patients was only 4.6%. These results agreed with the Boston Collaborative Drug Surveillance Program, which found a similarly low mortality rate from digitalis intoxication.⁶ Mahdyoon et al⁵ concluded that, in fact, the incidence of accurate diagnoses was much lower than reported and in their own series, 60% of patients diagnosed with toxicity were only possibly suffering from digoxin and 20% had no evidence to support the diagnosis at all.

The most extensive contemporary study of the therapeutic use of digoxin is that of the Digitalis Investigation Group (DIG), which surveyed 7000 patients in 302 centers in the United States and Canada who had low left ventricular ejection fractions (LVEF <0.45). A series of investigations showed that the medication had no effect on cardiovascular or all-cause mortality, but reduced the incidence of hospitalization ($P < 0.001$) and the incidence of death caused by worsening heart failure ($P < 0.06$). The sicker the patient (LVEF <0.25), the greater the improvement with digitalization.

One of the chief investigators of the DIG trials, Milton Packer,⁷ points out that the DIG’s studies concluded that the drug was effective in relieving the symptoms and signs of congestive heart failure and remained an “effective, safe and inexpensive choice for the relief of symptoms.” He also commented, however, that other drugs used to treat congestive heart failure not only relieved symptoms but prolonged life (such as the angiotensin-converting enzyme [ACE] inhibitors and β -blockers) in these patients.

In a post hoc subgroup analysis of the DIG data, Figueiredo and Machado⁸ addressed Rathore et al’s⁹ findings that women randomly assigned to treatment with digoxin in the DIG survey had a higher rate of death than those in the placebo group, although men showed no difference when treated with the drug compared with those who were not. Figueiredo and Machado suggested that the impact on women may well have been due to digitalis intoxication, because high serum concentrations of the drug (serum levels ≥ 2.0 ng/mL) were present in 2.3% of men but in 3.4% of women a month after randomization. (At a serum level of 2.5 ng/mL, the incidence of arrhythmia is 50% and increases with increasing blood levels of the drug.¹⁰)

Rathore et al⁹ discount this idea, suggesting that the difference in mortality might be due to an interaction between hormone replacement (specifically, with progesterone) and digoxin, because progesterone reduces renal excretion of digoxin. Unfortunately, the DIG investigators did not correlate their data with the use of hormone replacement therapy, so the question remains unanswered. Domanski et al¹¹ note that a randomized trial of digitalis therapy in women with heart failure, although needed, has not and will

probably never be performed. The authors performed a secondary analysis of data on patients entered into the Studies of Left Ventricular Function (SOLVD) trial and concluded that there was no significant gender-based difference in patient survival for those treated with digitalis.

To my mind, Brophy's¹² comments are the most thoughtful and on target of any as to why we should continue to use this effective, well tested, and inexpensive medication in patients suffering from congestive heart failure. He believes that the post hoc studies may not be sound enough to warrant abandoning digoxin because of the assertion that it fails to decrease mortality and, in fact, increases that of treated women—the studies were not randomized to specific digoxin concentrations and physicians had the option of adjusting the treating dose as clinically indicated. "A substantial bias would be introduced if patients who are the most ill systematically received the highest digoxin doses," he writes. He reminds us that the DIG studies emphasized the significant improvement digoxin makes in morbidity and in the incidence of hospitalizations for worsening failure in treated patients. Brophy wonders whether or not the pharmaceutical companies' intensive marketing efforts for newer therapies might be in part responsible for the fact that although prescription rates for evidence-based remedies to improve failure are not as high as we would like, those for digoxin are significantly lower (eg, digoxin is currently prescribed at only 50% of the frequency with which ACE inhibitors are dispensed).

Cleland and Cullington¹³ support Brophy's point of view. In a recent editorial, they remark that the benefits of newer medications like ACE inhibitors, β -blockers, and aldosterone antagonists might be so profound that they swamp additional benefits from using digoxin in combination with these entities. But, the authors say:

"We are simply not doing as well (in treating congestive heart failure) as some people would like to think. A combination of better monitoring, improved pharmacological interventions, more aggressive device strategies, and ultimately replacement of organ function or, alternatively, improved palliative care will be required to manage the growing size and complexity of the population with heart failure."

It seems to me that while it is entirely reasonable to utilize novel and effective treatments for disease, all too often we abandon older, cheaper, less well marketed and publicized agents in the process. There is certainly a place for digoxin in the amelioration of congestive heart failure: it is affordable (much less expensive than an ACE inhibitor), it produces a substantial benefit in morbidity, and, if added to new agents, it might make a significant difference in the success of patient therapy. Every effort should be made to test digoxin's effectiveness with other agents and to examine the impact of doing that on survival and quality of life in the treatment of this debilitating, fatal disease. New is not necessarily better, and sometimes 50-year-old papers are as valuable as those we pull from the Internet today. We are fascinated with the "latest" data and often don't even consider studies that are over a decade old. But the exquisite description of how this simple botanical cured the symptoms and signs of even far advanced myocardial failure is as relevant and accurate today as it was more than 200 years ago. We should teach our students and colleagues that digoxin still has a vital place in the therapeutic armamentarium.

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