Current Concepts in DIGITALIS THERAPY

A guide to the use of digitalis drugs

by BERNARD LOWN, M.D.
and SAMUEL A. LEVINE, M.D.

Current Concepts in

DIGITALIS THERAPY

By

BERNARD LOWN, M.D.
Formerly Assistant in Medicine,
Peter Bent Brigham Hospital

and

SAMUEL A. LEVINE, M.D.
Clinical Professor of Medicine,
Harvard Medical School;
Physician, Peter Bent Brigham Hospital

LONDON
J. & A. CHURCHILL LTD.
104 GLOUCESTER PLACE, W.1
1955

PRINTED IN THE UNITED STATES OF AMERICA

AND PUBLISHED IN BOSTON BY

LITTLE, BROWN AND COMPANY

34 BEACON STREET

Acknowledgments

The authors wish to express gratitude and acknowledge indebtedness to the following, who aided in the prosecution of these studies:

Dr. M. G. Criscitiello
Dr. A. T. Crocker
Dr. J. G. Gros
Dr. R. Hoigne
Dr. H. D. Levine
Dr. H. J. Levine
Dr. J. P. Merrill
Dr. J. P. Vazifdar
Dr. J. M. Weller
Dr. N. F. Wyatt
Mr. W. Elliott
Miss Eunice Gilman

CONTENTS

Current Concepts in

DIGITALIS THERAPY

CHAPTER I

Introductory Remarks

THE use of digitalis marks the beginning of the modern era of cardiac therapy. Whole-leaf digitalis and the purified derivatives, the cardiac glycosides, continue as the most effective medicinal agents in the management of patients with congestive heart failure. The loss of cardiac reserve manifested by failure is the result of an imbalance between cardiac muscle strength and the work load imposed on the heart. Therapy is therefore directed toward improving the function of the failing heart muscle and reducing the work load on the myocardium. The two are intertwined; affecting one influences the other. Since the ultimate event in the chain leading to clinical failure occurs within the heart, the main therapeutic goal is to improve the vital function of the heart in propelling blood. The digitalis drugs are the only agents known to restore compensation through such direct action on the myocardium. All other measures are ancillary. The need for these supplementary measures in a given case varies inversely with the efficacy of digitalis.

During the last decade intensive study of the pathogenesis of one of the features of congestive heart failure — namely, edema accumulation — has focused attention on the kidney. A glomerular tubular imbalance has been suggested as the critical factor in the formation of cardiac edema.[1,2] Emphasis on the

role of the kidney in increasing the cardiac load through salt and water retention has brought about a deviation from the concept of the primacy of the heart in initiating and sustaining failure. A stage has been reached at which arguments are being advanced to reassign to the heart the major role in the complex drama of congestive heart failure. The tendency to regard failure as the consequence of renal impairment has had therapeutic implications. As a result therapy is sometimes based exclusively on salt manipulation achieved through various regimens of dietary salt restriction, interference with intestinal sodium absorption and the promotion of renal salt loss. The mercurial diuretic and the weighing scale have been proposed as the vital implements for managing congestive heart failure.[3]

Recognition of the inseparable interaction of cardiac and extracardiac factors in the pathogenesis of failure must guide therapy. Translated into practice this means that digitalis is useful, with but few exceptions, during the entire course of the evolution of cardiac failure. In the early stages major reliance is placed on digitalis. Measures that diminish heart work, however, are not neglected. As decompensation advances and digitalis no longer overcomes the deterioration in cardiac competence, emphasis shifts to the restriction of salt intake and the promotion of salt loss. In the initial phases of decompensation the aim of therapy is to improve the function of the heart for the requirements of normal life. In the later phases the goal is to diminish the heart's burden and to bring it within the domain of limited cardiac performance.

As in Withering's day, the proper use of digitalis

presents many problems. Questions of when and how to administer the drug as well as how to determine the adequacy of maintenance dosage are not yet fully answered. During the past three years new data on the action of digitalis have been acquired in our laboratory. In this report some of our work and the relevant studies of others are reviewed. These are considered from five points of view: the mode of action of digitalis and the clinical indications for its use; the toxic properties common to all therapeutically active digitalis-like preparations; the changes in the toxic threshold after alterations in body electrolytes; atrial arrhythmias frequently resulting from overdosage; and a method for predicting digitalis requirement for maximum therapeutic effect before digitalization.

CHAPTER II

The Action and Clinical Use of Digitalis in Heart Failure

Extracardiac Effects

The rational use of digitalis requires an understanding of its action on human cardiovascular dynamics. The effectiveness of digitalis in heart failure has been attributed to direct cardiac as well as extracardiac actions. Withering was impressed with the diuretic properties of digitalis and attributed improvement to drug action on the kidneys.[4] His contemporary, John Ferriar, was the first to conclude that the essential quality of the plant was exerted on the heart. Present-day concept is in accord with Ferriar's[5] view and holds that mobilization of edema is secondary to improved cardiac function.

Recent studies with Digoxin, however, show that this glycoside has a moderate but definite diuretic action.[6] In patients without edema or with noncardiac edema a slight increase in salt and water excretion follows its administration. When normal persons are given desoxycorticosterone acetate (DOCA) and an increased salt intake until edema forms, Digoxin induces a profound diuresis comparable qualitatively and quantitatively to that observed in congestive heart failure. In none of these subjects did digitalization produce alterations in renal or cardiac hemodynamics. Digoxin may therefore exert a direct effect on the renal tubules. Presumably, the drug depresses

sodium reabsorption by competition with a DOCA-like adrenal steroid that it resembles in chemical configuration.[6] In ordinary clinical failure the improvement that occurs with digitalization frequently precedes and at times is not associated with any significant diuresis. This suggests that if a direct renal factor is operative it is in all likelihood subsidiary to the effect of digitalis on the cardiovascular system.

Is the clinical value of digitalis derived from a peripheral or central action on the cardiovascular apparatus? The reduction in venous pressure and the enhanced cardiac output after digitalization resemble the changes produced by tourniquet application or phlebotomy. McMichael and Sharpey-Schafer[7] therefore concluded that digitalis acts through venoconstriction. They reasoned that, by augmenting peripheral venomotor tone, digitalis lowered venous pressure, decreased venous return and lessened the overload on the heart. The result was a more efficient contraction and more complete emptying of the heart.

When ouabain was the glycoside tested the same observers found that in half the cases of heart failure there was a definite increase in cardiac output without associated changes in venous pressure. This indicated direct stimulation of the heart.[8] Others utilizing cardiac-catheterization technics found no relation between the magnitude of fall in venous pressure and the degree of increase in cardiac output. Furthermore, the increased cardiac output preceded the fall in the central venous pressure.[9] Similar studies in patients with isolated failure of the left ventricle demonstrated that with digitalization there was a significant increase in cardiac output and stroke volume

accompanied by a decrease in pulmonary arterial pressure. These were achieved without alterations in right-ventricle end-diastolic pressure and could not be ascribed to the action of the drug on systemic venous pressure.[10]

Cardiac Action

Effect on the heart rate. In general there are two concepts of the mode of digitalis action on the heart. One school considers that restoration of compensation is an indirect effect mediated through reduction in rate, and the other attributes it to direct action upon the myocardium. Mackenzie[11] and Lewis[12] ascribed the benefits to depression of atrioventricular conduction and vagal slowing of the heart rate. Digitalis was therefore restricted to patients with atrial fibrillation and a rapid ventricular response. The larger number of patients whose failure was accompanied by regular rhythm frequently were not treated with digitalis. Such a view is no longer tenable. Extensive clinical data attest to the fact that patients with normal sinus mechanism are strikingly benefited. Experience with cardiac catheterization in failure demonstrates similar hemodynamic changes after digitalis irrespective of the underlying rhythm. It is now generally believed that, with the exception of certain atrial arrhythmias, slowing of the heart rate is the result of restored compensation rather than the converse. In patients with sinus rhythm digitalis may improve the clinical state before a material reduction of the heart rate. Therapeutic doses slow a rapid heart only in the presence of failure. When increased rate occurs without decompensation, as in the sinus

tachycardias of fever, anemia and thyrotoxicosis, digitalis is notoriously ineffective.

Atrial fibrillation may be an exception when rate reduction per se is a significant factor contributing to improvement. In patients with atrial fibrillation, who are highly susceptible to rate fluctuations, the ventricular rate reflects the state of compensation. When failure is accompanied by fibrillation with a rapid ventricular response, slowing invariably occurs with restored compensation. That rate reduction alone is a significant factor is indicated by the following observation. Occasionally, a patient with mitral stenosis and pulmonary congestion, having normal sinus rhythm, fails to improve on digitalis only to show a distinct clinical improvement with the onset of atrial fibrillation. This change for the better may take place on the same dose of digitalis if the ventricular rate after the onset of fibrillation becomes slower than it was with sinus rhythm. This apparently results from the ability of the drug in this instance to slow the ventricles when the atria are fibrillating, in contrast to its failure to do so when the rhythm is regular.

Two mechanisms are operative in slowing the heart.[13] When small doses of digitalis are administered slowing is mediated by the vagus nerve and may be abolished by atropine or exercise. As the dose is increased, extravagal factors predominate. The resting rate with small or large doses of digitalis may be the same. When the slowing is merely vagal, however, physical exertion causes exaggerated acceleration of the heart.[14] These facts account for the observation that further improvement may be achieved after more digitalis without rate alteration. In pa-

tients with atrial fibrillation rate response to exercise serves as an effective gauge to the adequacy of therapy. Such a clear-cut indicator is absent in patients with normal sinus rhythm. This is in part responsible for the belief that digitalis is effective only in patients with atrial fibrillation.

Myocardial Action

The major pharmacologic effect of digitalis is its direct action on the myocardium. Digitalis increases the force of systolic contraction of heart muscle,[15] without alteration in the diastolic fiber size. The more forceful contraction results in more complete ventricular emptying with a rise in volume output. There is also an enhanced capacity to propel blood against increased peripheral resistance.[16] At the same time the duration of systole is abbreviated, allowing greater time for both ventricular filling and heart rest.[17] The diastolic size of the heart is reduced.[18] Since oxygen consumption is a function of the initial diastolic fiber length[19] such a reduction in size diminishes the oxygen expenditure for any work output.[20] The work capacity of the heart is increased, and a greater percentage of the liberated energy, therefore, is used in the mechanical processes of shortening and development of tension. The over-all result is an increase in cardiac efficiency and output. The basic pattern of myocardial derangement that characterizes failure is thus reversed. In other words the digitalized failing heart can do the same work with less energy (oxygen utilization) or more work with the same energy expenditure than before digitalization.