Studies on Digitalis

III. The Influence of Triiodothyronine on Digitalis Requirements

By Robert L. Frye, M.D., and Eugene Braunwald, M.D.

There has been considerable interest in whether or not changes in the thyroid state modify the effectiveness of digitalis. A number of reports have suggested that patients with hyperthyroidism associated with congestive heart failure or atrial fibrillation are relatively unresponsive to the usual doses of digitalis.1-8 Others have indicated, however, that these patients may respond to the ordinary dose of digitalis.9-11 Some observers5 have advocated that great caution should be exercised in administering digitalis to patients with thyrotoxicosis, and the possibility that digitalis may result in myocardial necrosis in hyperthyroidism has been suggested by experimental studies.12

These widely varied views are based primarily on clinical impressions. The present investigation was therefore designed to evaluate, in quantitative fashion, the changes in digitalis requirements that follow alteration of the thyroid state induced by triiodothyronine administration. In addition, an attempt was made to elucidate the mechanism involved in the observed changes in digitalis requirements. Portions of this study have been presented elsewhere in preliminary form.13

Methods

Six patients with inactive rheumatic heart disease and one patient (F.G.) with arteriosclerotic heart disease were studied; these patients ranged in age from 20 to 60 years and all had chronic atrial fibrillation. None of the patients was in congestive heart failure at any time during the investigation. One patient (J.D.) had been rendered myxedematous by means of I131-induced thyroid ablation for congestive heart failure, which had existed 2 years prior to this study. One patient had spontaneous myxedema.

Alterations of the metabolic state were induced by the daily oral administration of 75 to 500 μg. of triiodothyronine (T3) in divided doses, or by a single intravenous injection of this drug. The effects of this medication on heart rate, basal metabolic rate, serum cholesterol, and protein-bound iodine were noted. In all patients in whom hyperthyroidism was induced by means of oral T3, an increase in nervousness, fatigability, and sweating was observed. The ventricular rate was utilized to provide a quantitative expression of digitalis effect throughout these studies. In all but the first patient described below, the resting ventricular rates were determined each morning for a 2-minute period after the patient had been in the recumbent position for 30 minutes.

Experimental Procedures and Results

I. J.D., a myxedematous patient with rheumatic heart disease and chronic atrial fibrillation, was studied by determining the manner in which the administration of T3 altered the amount of acetylstrophanthidin required to achieve a given reduction in ventricular rate. The individual determinations of acetylstrophanthidin requirement were performed in a constant manner. On arrival in the laboratory the patient remained at complete rest in bed for 15 minutes, during the last 10 minutes of which the control ventricular rate was recorded. In this particular patient attempts were made to minimize the vagal effects of digitalis and to provide a comparable starting ventricular rate at various levels of T3 dosage. This was accomplished by atropine sulfate, which was administered intravenously in a dose ranging from 0.50 mg. to 1.0 mg. When the patient was myxedematous and the control ventricular rate was low, the dose of atropine was 1.0 mg. After the administration of T3, however, as the patient became euthyroid, the dose was lowered to 0.50 mg. Immediately following this injection, a continuous infusion of 0.018 mg. per minute of atropine sulfate was begun and was maintained by means of a Bowman infusion pump through-
out the remainder of each study. This procedure made it possible for the ventricular rates to be in a comparable range (av. = 92 beats per minute) at the onset of each acetylstrophanthidin infusion. Thirty minutes following the initial injection of atropine, an acetylstrophanthidin infusion was begun at a rate of .03 mg. per minute by means of a second Bowman infusion pump, and the ventricular rate was recorded electrocardiographically during every alternate minute. The amount of acetylstrophanthidin required to reduce the ventricular rate to 70 per minute and the amount necessary to result in an absolute reduction in the ventricular rate of 20 beats per minute were determined.

Figure 1 illustrates the response of the patient to the infusion of acetylstrophanthidin when he was myxedematous, and also after he had been rendered euthyroid with 75 μg. of T3 daily. It is evident that in order to produce a comparable decrease in ventricular rate, the acetylstrophanthidin had to be infused for only 16 minutes, a total of 0.48 mg., when the patient was myxedematous, whereas a 50-minute infusion, i.e., a dose of 1.50 mg., was required when he was euthyroid.

The results of the entire study are presented in figure 2. When the patient was hypothyroid, the amount of acetylstrophanthidin required to reduce the ventricular rate to 70 per minute ranged from 0.48 to 0.72 and averaged 0.58 mg. At this time 0.48 mg. to 0.72 mg. (av. = 0.54 mg.) of acetylstrophanthidin was required to reduce the ventricular rate by 20 beats per minute from the rate existing at the time the infusion was begun. After the patient had been rendered euthyroid by the administration of 75 μg. per day of T3, the serum cholesterol fell and the control ventricular rate rose. The acetylstrophanthidin required to reduce the ventricular rate to 70 per minute increased to 1.50 mg. and the amount necessary to result in an absolute reduction in ventricular rate of 20 beats per minute increased to 0.84 mg. Three to 4 weeks after the T3 had been discontinued the acetylstrophanthidin requirement fell to the levels that were observed prior to the T3 administration, and the cholesterol and control ventricular rates returned to their previous levels.

II. One myxedematous and three euthyroid patients were studied by determining the resting ventricular rates each morning while they were on a constant maintenance dose of oral digoxin. T3 was then administered at a constant dose to each patient, this dose ranging from 100 to 250 μg. per day. After the T3 effect had stabilized, and while the drug was continued, the additional amount of oral digoxin required to reduce the ventricular rate to control levels and to maintain it at these levels was determined. Both in patients C.C. (fig. 3) and S.C. the dose of digoxin during the control period was 0.20 mg. and in order to return the ventricular rate to control levels during the T3 administration, the daily dose of digoxin had to be increased to 0.90 mg. In patient C.C. (fig. 3) the dose had to be maintained at this elevated level in order to maintain the ventricular rate at control levels. In patient W.P. a total of 2.30 mg. of digoxin, administered over a 2-day period, was necessary to return the ventricular rate to control
Observations on acetylstrophanthidin requirements before, during, and after T3 administration in patient J.D. In the lowest panel, the points joined by the broken line represent the dose of acetylstrophanthidin required to reduce the ventricular rate to 70 beats per minute, while the points joined by the solid line represent the dose required to reduce the ventricular rate by 20 beats per minute from the rate existing at the time the infusion was begun. The control ventricular rate represents the basal rate prior to the atropine administration.

levels, and a daily dose of 0.80 mg. per day was required to maintain the ventricular rate at control levels. When the daily dose was lowered to 0.40 mg. per day, the ventricular rate rose again. In all three patients, the relatively large doses of digoxin that were administered were tolerated without evidence of toxicity.

In the myxedematous patient (C.E.) the increased ventricular rate during T3 administration was reduced only slightly by increasing the daily oral dose of digoxin from 0.25 mg. to daily doses ranging between 0.65 and 1.37 mg. and averaging 1.05 mg. The total dose of digoxin required to return the resting ventricular rate to the control level could not be assessed, since this patient developed gastrointestinal manifestations of digitalis intoxication.

III. Three euthyroid patients were studied by determining their morning ventricular rates first while they were on a constant dose of oral digoxin and then after they had also been given T3. Reserpine or syrosingopine was then administered intramuscularly and the changes in ventricular rate were noted while the same doses of digoxin and T3 were continued. In all three patients the ventricular rate returned to the levels that existed before the administration of T3 without additional digoxin (fig. 4).

IV. Two euthyroid patients who were maintained on a constant daily dose of digoxin were studied by noting the change in the daily ventricular rate after an intravenous injection of T3. These observations were made both before and after the administration of syrosingopine. In one patient (F.G., fig. 5) the increase in ventricular rate resulting from T3 was almost completely prevented by syrosingopine, while in the other patient (C.C.) it was partly prevented.

Discussion

These results indicate that T3 increases the digitalis requirements in patients with chronic atrial fibrillation and thus they are in agreement with those observations suggesting that hyperthyroid patients with atrial fibrillation do not respond in a normal fashion to the usual doses of digitalis.1, 2, 4 The present study permitted a quantitative estimation of the alterations in digitalis requirement associated with variations in the thyroid state. The induction of mild thyrotoxicosis in patients with chronic atrial fibrillation resulted in a
three- to four-fold increase in the dose of digitalis required to maintain the ventricular rate at the level that was present in the euthyroid state. Similarly, the induction of a euthyroid state in previously hypothyroid patients also resulted in an increase in digitalis requirements. These augmented digitalis requirements resulted not only from an increase in the resting ventricular rate, but also from the larger doses needed to achieve any given amount of slowing of the ventricular rate during T₃ administration (figs. 1 and 2).

Throughout this study the slowing of the ventricular rate in patients with atrial fibrillation was utilized to provide a clinical index of digitalis effect. This procedure is similar to that employed by Gold and his collaborators for comparing the onset and duration of action of various glycosides. In patients with atrial fibrillation the ventricular rate is largely determined by the refractory period of the atrioventricular node, and the action of digitalis glycosides in prolonging this refractory period is well established. Woodbury and Hecht, however, in studies with single heart muscle fibers, have demonstrated a dissociation of electrical and mechanical effects of glycosides. Hemodynamic studies have also suggested that in patients with atrial fibrillation the positive inotropic action of the glycosides is not necessarily reflected precisely by the slowing of the ventricular rate.

It was evident that when large doses of digitalis were administered the tachycardia resulting from T₃ administration could be abolished, and it was of interest that manifestations of digitalis intoxication occurred in only one of the patients who was given these large amounts of the drug. Thus, the observations presented herein are not consonant with the view that digitalis is of little value in controlling the ventricular rate of hyperthyroid patients with atrial fibrillation. Although it has been suggested that digitalis should be administered with great caution to patients with thyrotoxicosis, it is difficult to determine the susceptibility of these patients to digitalis intoxication. In addition to atrial fibrillation, a variety of arrhythmias, including premature beats, heart block, and ventricular tachycardia, have been described in undigitalized hyperthyroid patients, thus making it difficult to evaluate the role of digitalis in producing such disturbances in rhythm and conduction. Although the possibility that digitalis administration is hazardous in the presence of hyperthyroidism was suggested by a study in which this drug was reported to produce areas of myocardial degeneration in hyperthyroid cats, these results cannot be readily transferred to man.

The mechanism of the observed increase in digitalis requirements with T₃ administration is not clear. It is certainly possible that changes in the thyroid state modify the metabolism or inactivation of digitalis. It was evident, however, that both reserpine and syrosingopine abolished these increased digitalis requirements (figs. 4 and 5). It is now well established that these rauwolfia alkaloids deplete a variety of tissues of their stores of

Figure 4
Effect of T₃ on the ventricular rate of a patient on a constant dose of digoxin, and the reversal of this effect by syrosingopine. The graph is interrupted from the tenth to the eighty-fifth day of the study, during which the T₃ dosage was gradually increased until clinical evidence of hyperthyroidism was evident.

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norepinephrine.26-30 However, syrosingopine is only one-tenth as active as reserpine in depleting the brain of amines, although it is as effective in depleting the heart's stores of norepinephrine.31 This difference in action of the two drugs is thought to be the basis for the significant sedative and depressive effects noted with reserpine and the absence of these effects with syrosingopine. Thus, it may be postulated that the abolition by reserpine or syrosingopine of the T3-induced augmentation of digitalis requirements is related to the depletion of norepinephrine from the heart and is independent of any sedative effects. This hypothesis receives support from the experiments of Brewster et al.,32 who demonstrated in dogs that total sympathetic blockade prevented the metabolic and hemodynamic effects of thyroid feeding. Both reserpine and syrosingopine, however, also possess parasympathomimetic actions,33 which could also have been responsible for the prevention of the T3-induced augmentation of digitalis requirements.

In spite of a lack of complete understanding of its mechanism of action, reserpine has been administered to patients with thyrotoxicosis and has resulted in an amelioration of the signs and symptoms, including the hypermetabolism and tachycardia.34,35 Reserpine has also recently been demonstrated to have a bradycrotic effect in euthyroid patients with atrial fibrillation.36 Thus, in the clinical management of hyperthyroid patients with atrial fibrillation and a rapid ventricular rate, it would seem appropriate to utilize both digitalis and syrosingopine. The latter drug would be useful in decreasing the digitalis requirements in such patients and should thus eliminate the need for large doses of digitalis. The syrosingopine should be administered intramuscularly in order to obtain the prompt effects that are desired in such a clinical situation, since after the initiation of oral therapy the bradycrotic effects are not apparent for several days.36 It must, however, be emphasized that syrosingopine or reserpine does not eliminate the need for specific antithyroid therapy.

**Summary**

The effects of triiodothyronine (T3) administration on digitalis requirements was studied in a group of patients with atrial fibrillation. The ventricular rate was utilized to provide a quantitative expression of digitalis effect. In one patient the amount of acetylstrophanthinidin, administered as a constant infusion, required to slow the ventricular rate to 70 beats per minute rose from an average of 0.58 mg. while he was myxedematous, to 1.50 mg. when he was euthyroid.

When mild thyrotoxicosis was induced in three euthyroid patients the daily dose of digoxin had to be increased approximately four-fold in order to maintain the ventricular rate at a control level. In three patients it was observed that reserpine or syrosingopine administered intramuscularly abolished the increased requirements for digoxin induced by T3. In two patients syrosingopine was found to prevent partially the tachycardia resulting from large doses of intravenous T3. The possible mechanisms responsible for these effects and their therapeutic implications are discussed.
References


Quite as interesting as the advance in our control of disease, and perhaps as significant for the future, our interpretation of disease, and consequently our ways of reacting to it, have changed. In the past more than once they have changed, and usually in the direction of a less superstitious and more rational attitude. As the concept of disease has become more rational, it has involved, in one form or another, the recognition of how wise it is for the individual to be concerned with the health of others, as an aid to his own safety. Scientific knowledge of communicable disease demonstrated beyond any question the social aspects of individual illness, and the importance to one and all of a healthy common environment.—Alan Gregg, M.D. Challenges to Contemporary Medicine. New York, Columbia University Press, 1956, p. 80.
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ROBERT L. FRYE and EUGENE BRAUNWALD

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