Cardiac arrhythmias induced by hypokalaemia and potassium loss during maintenance digoxin therapy

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Twelve patients with congestive heart failure receiving maintenance therapy with digoxin and potent diuretics were followed closely during development of hypokalaemia and potassium loss. Cardiac arrhythmias compatible with digoxin toxicity developed in 6 patients in the presence of stable, normal serum digoxin concentrations. The mechanisms involved in the development of the rhythm disturbances are discussed with regard to hypokalaemia, intracellular potassium loss, intra-/extracellular potassium gradients and digoxin, and the significance of maintaining a normal potassium balance in this setting is stressed.

It is generally accepted that hypokalaemia and potassium loss may promote digitalis toxicity in patients with congestive heart failure receiving maintenance treatment with digitalis. However, while this situation was frequent in earlier studies of digitalis toxicity (Lown and Levine, 1954; Jorgensen and Sorensen, 1970), hypokalaemia and potassium loss were not observed as causes of digitalis intoxication in more recent reports (Beller et al., 1971; Evered and Chapman, 1971). Though this new trend may reflect better treatment with regard to maintenance of potassium balance during digitalis therapy in particular in patients on chronic diuretic therapy, it seems also possible that the risks involved in hypokalaemia and potassium loss in this setting have been overestimated in the past. In earlier studies of digitalis toxicity in man the relative role of digitalis overdosage and of acute or chronic hypokalaemia or potassium loss have not been precisely defined, and more recent studies in dogs have not supported the concept that hypokalaemia sensitizes the myocardium to digitalis during conditions representing the nearest practical approximation to the situation of patients on chronic diuretic therapy (Kleiger, Vitale, and Lown, 1965; Binnion, 1975).

In an attempt to clarify the significance of hypokalaemia and total potassium deficiency and to evaluate the role of serum digoxin levels in this setting, the present study was planned. Twelve patients with advanced heart failure receiving maintenance therapy with digoxin and potent

diuretics were subjected to a potassium depleting regimen and followed closely for development of cardiac arrhythmias while serum digoxin concentrations were controlled.

Methods

Twelve patients with advanced congestive heart failure admitted to Medical Department B, Rigshospitalet Copenhagen, were selected for study according to the following criteria: 1) The subjects had received maintenance digoxin therapy for at least one month and showed normal serum digoxin levels, 2) the patients were in a stable situation on maintenance diuretic treatment, and 3) the subjects presented normal serum potassium concentrations and were apparently in a stable potassium balance while receiving a standard supplement of potassium chloride of 3 g daily or a potassium sparing drug as additional diuretic if required. The series consisted of 5 men and 7 women; mean age 57·7 years. The clinical diagnoses were rheumatic valvular disease in 6 patients, ischaemic heart disease in 4, and cardiomyopathy in 2. The patients received maintenance treatment with digoxin in a dose range from 0·125 to 0·50 mg daily and frusemide 80 to 160 mg or bumetanide 4 to 6 mg per day.

With their informed consent the patients were studied according to the following plan: the electrocardiogram was monitored continuously permitting rapid discontinuation of the study and restoration of potassium balance if required. The maintenance therapy with digoxin and potent diuretics was continued while potassium chloride and potassium sparing drugs were withheld. The patients were studied on a metabolic regimen including a diet restricted in potassium (30 mEq daily). Twenty-four hour urinary volumes and excretion of

potassium were measured. Body weight was determined every morning. At the start of the study total exchangeable potassium (K_e) was measured by dilution with K^{42} (Olesen, 1964). Serum potassium and creatinine were determined every morning (normal range for serum K: 3·5–5·1 mmol/l). Serum digoxin was measured in the fasting state at the start and the end of the study (Steiness, 1974). The study was planned to last 7 days for each patient, but was interrupted immediately if significant arrhythmias occurred.

Serum thyroxine was measured in 10 patients and found to be within the normal range.

Calculation of potassium balance

The cumulative balance of potassium was determined as summations of daily intakes—renal outputs corrected for faecal and insensible losses (Isaksson, Lindholm, and Sjogren, 1966; Maronde, Milgrom, and Dickey, 1969). The cumulative negative potassium balance was partitioned into extra- and intracellular losses, and the intra-/extracellular potassium gradients were derived as follows.

a) Abbreviations ECW = total extracellular water, $(K)s$ = serum potassium concentration, ECK = total extracellular potassium, ICK = total intracellular potassium, K_e = total exchangeable potassium (assumed to represent initial body potassium), K_{ic} = intracellular potassium concentration, ICW = total intra-cellular water, '1→n' indicates the cumulative 24-hour periods of investigation.

b) Starting values ECW_0 = body weight$_0$ × 0·3, ECK_0 = ECW_0 × $(K)s_0$, ICK_0 = K_e − ECK_0, ICW_0 = $ICK_0/160$, gradient$_0$ = $K_{ic0}/(K)s_0$. The basic assumption was made that the average intracellular K concentration of the body and of the myocardium was 160 mmol/l. at the start of the study (Valentin and Olesen, 1973).

c) Cumulative balance values ECK_1→n = $(ECW_0$−weight loss$_{1→n}$) × $(K)s_{1→n}$, ΔECK_1→n = ECK_1→n, ECK_0, ICK_1→n = ICK_0 + (ΔK balance$_{1→n}$ −

ΔECK_1→n), ΔICK_1→n = ICK_1→n − ICK_0, K_{ic1}→n = ICK_1→n/ICW_0.

Intra-/extracellular potassium gradients were calculated according to two models. *Model I:* gradient I_1→n = K_{ic1}→n/$(K)s_1$→n, Δgradient I_1→n = gradient I_1→n − gradient I_0. *Model II:* gradient II was calculated as shown above under the assumption that the myocardial intracellular potassium concentration remained unchanged during the study (Bolte, 1973).

Interpretation of electrocardiogram

The continuous monitoring of the electrocardiogram and tracings of one minute's duration taken at least twice daily were analysed for arrhythmias, usually ascribed to digoxin toxicity (Evered and Chapman, 1971).

Results

Cardiac arrhythmias occurred in 6 out of 12 patients (50%) within the week of the study. Four patients developed ventricular premature beats either as multifocal ectopic beats or as bigeminy. Two patients showed atrial premature beats with prolonged PQ intervals. All 6 patients showed hypokalaemia and overall potassium loss when the arrhythmias occurred. In 2 patients interruption of the study became necessary after 3 and 4 days because of the development of rhythm disturbances. In the remaining 4 patients the arrhythmias only occurred on the last day of the study.

Serum digoxin concentrations showed a mean value of 1·52 ± 0·17 nmol/ml (1·19 ± 0·13 ng/ml) at the start of the study and did not change significantly during the experiment. The daily oral dose of digoxin was 0·30 ± 0·06 mg. As shown in Table 1 the mean values and the trends were exactly the same in the group developing arrhythmias and in the group without. Similarly, serum creatinine concentrations were the same in the two groups and remained unchanged during the study.

TABLE 1 *Summary of data in patients on maintenance digoxin therapy (mean values ± SEM)*

	No.	Age (yr)	Average daily digoxin dose (mg)	Serum digoxin concentration (nmol/ml)		Serum creatinine concentration (mmol/l)	
				Before	After	Before	After
All subjects	12 M:5, F:7	57·7 ±3·7	0·30 ±0·06	1·52 ±0·17	1·69 ±0·23	0·11 ±0·01	0·11 ±0·01
Subjects developing arrhythmias	6 M:2, F:4	59·5 ±3·9	0·28 ±0·04	1·51 ±0·29	1·63 ±0·37	0·11 ±0·01	0·11 ±0·01
Subjects not developing arrhythmias	6 M:3, F:3	55·8 ±6·6	0·32 ±0·05	1·54 ±0·18	1·77 ±0·23	0·11 ±0·02	0·11 ±0·01

Conversion from SI to traditional units: digoxin 1 nmol≈0·78 ng.

TABLE 2 *Summary of data on potassium balance (absolute values given as mean values ± SEM)*

	No.	Serum potassium (mmol/l) Before	After	Total exchangeable potassium (mmol)	Total K balance (mmol)	Total extracellular K balance (mmol)	Total intracellular K balance (mmol)
All subjects	12	4·37 ±0·10	3·41 ±0·09	1890 ±125	−204 ±18	−21 ±2	−183 ±20
Subjects developing arrhythmias	6	4·45 ±0·13	3·45 ±0·15	1918 ±241	−204 ±26	−24 ±3	−180 ±27
Subjects not developing arrhythmias	6	4·28 ±0·17	3·37 ±0·13	1861 ±106	−204 ±32	−18 ±4	−184 ±31

Potassium metabolism

As shown in Table 2 the regimen used proved effective in reducing serum potassium concentration from a mean value of 4·37 mmol/l at the start to a mean of 3·41 mmol/l at the end of the study. The development of hypokalaemia was associated with a mean total potassium loss of 204 mmol. 21 mmol (or 10% of total potassium loss) originated from the extracellular phase while the remaining 183 mmol (or 90% of total potassium loss) was lost from the intracellular phase. The cumulative changes in potassium balance for 10 patients studied for a full week is shown in Fig. 1. Apparently, the decrease of serum potassium concentration and of total body potassium was most pronounced during the first 4 to 5 days of the study.

The degree of hypokalaemia and of total potassium loss obtained was very similar in the group developing arrhythmias to that in the group without (Table 2).

For the whole group the total potassium loss amounted to 11 per cent of initial body potassium (Table 3). Of particular significance is the fact that the total extracellular loss represents 26 per cent of the initial total extracellular potassium whereas the total intracellular loss amounts to only 11 per cent of the initial total intracellular potassium. The relatively larger loss from the extracellular phase results in a rise in the intra-/extracellular potassium gradient 1 (model I) for the whole body (Table 3 and Fig. 2). An even larger rise is seen in the myo-
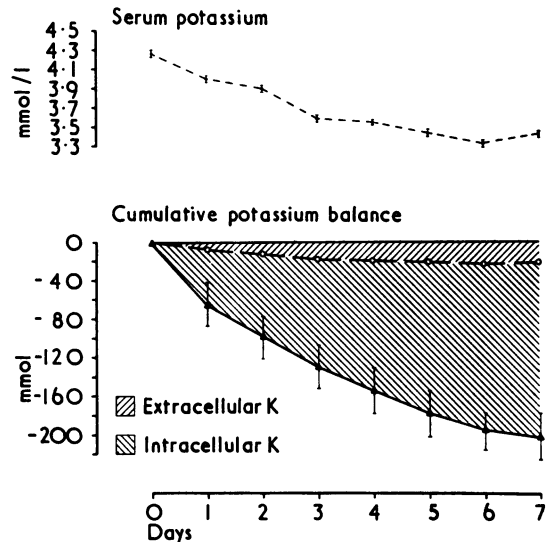

FIG. I *Serum potassium concentration and cumulative K balance in 10 patients receiving a K depleting regimen for 7 days. Mean values (±SEM) are given.*

TABLE 3 *Summary of data on potassium balance (relative values given as mean values ± SEM)*

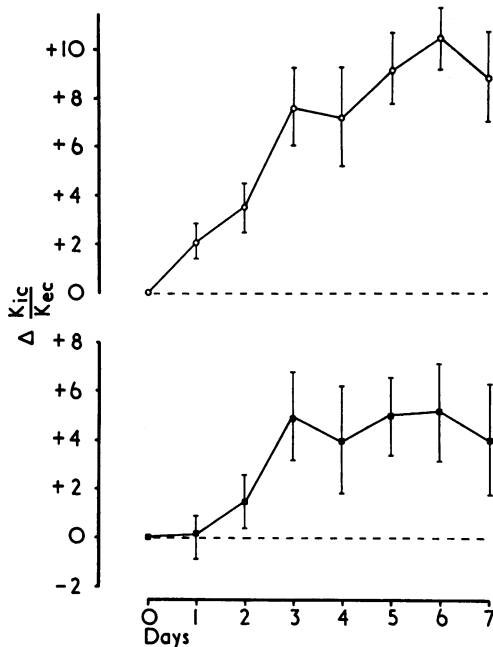|	No.	Total K loss as % of initial body K (%)	Total extracellular K loss as % of initial total extracellular K (%)	Total intracellular K loss as % of initial total intracellular K (%)	Change of intra-/ extracellular K gradient I	Change of intra-/ extracellular K gradient II
All subjects	12	−11·3 ±1·3	−26·1 ±2·1	−10·7 ±1·4	+4·2 ±1·8	+9·6 ±1·6
Subjects developing arrhythmias	6	−11·7 ±2·5	−28·1 ±1·7	−11·1 ±2·6	+4·6 ±1·7	+10·7 ±1·3
Subjects not developing arrhythmias	6	−10·8 ±1·3	−24·0 ±3·9	−10·3 ±1·3	+3·8 ±3·3	+8·5 ±3·2

FIG. 2 *Changes in intra-/extracellular K gradients in 10 patients receiving a K depleting regimen for 7 days. Mean values (±SEM) are given. The upper panel shows the myocardial K gradient (calculated on the assumption of an unchanged intracellular K concentration); the lower panel shows the K gradient for the whole body.*

cardial intra-/extracellular potassium gradient II (model II) which is derived on the assumption that myocardial intracellular potassium concentration remains unchanged while distinct hypokalaemia develops (Table 3 and Fig. 2).

The partitioning of the potassium loss and the changes in intra-/extracellular potassium gradients were the same in the group developing arrhythmias and in the group without (Table 3).

Discussion

The study was performed in patients with advanced congestive heart failure receiving maintenance digoxin therapy. The mean serum digoxin concentration was 1·52 ± 0·17 nmol/l (1·19 ± 0·13 ng/ml) at the start of the study and did not change significantly during the experiment. The average daily dose of digoxin was 0·30 ± 0·06 mg. In terms of serum digoxin values and daily digoxin doses our findings are in good agreement with other recent studies (Beller *et al.*, 1971; Carruthers, Kelly, and McDevitt, 1974).

In this setting 6 out of 12 patients developed cardiac arrhythmias fulfilling the criteria of digitalis toxicity. The arrhythmias occurred at serum digoxin levels which are usually not associated with toxic manifestations and were apparently precipitated by the development of chronic hypokalaemia and potassium loss.

There is evidence that *acute* hypokalaemia in patients given digitalis may provoke such arrhythmias as well after carbohydrate administration which displaces potassium from the extracellular to the intracellular phase as after potassium loss during haemodialysis (Page, 1955; Lubash *et al.*, 1959; Kunin, Surawicz, and Sims, 1962). The mechanisms of interplay between digitalis, hypokalaemia, and potassium loss are not clear, however. While in earlier dog experiments, acetyl strophanthidin produced rhythm disturbances at a lower dose after acute hypokalaemia induced by glucose and insulin infusion or haemodialysis than in normal dogs (Lown *et al.*, 1952; Kleiger *et al.*, 1965), this pattern was not reproduced in a recent study in acutely hypokalaemic dogs where digoxin was infused until atrioventricular dissociation occurred (Binnion, 1975). There is evidence that acute reduction of extracellular potassium concentration increases the ability of the myocardium to take up circulating digoxin (Cohn, Kleiger, and Harrison, 1967; Prindle *et al.*, 1969). However, the myocardial concentration of digoxin appears to be the same in normal and in acutely hypokalaemic dogs at the time of digitalis induced ventricular tachycardia or atrioventricular dissociation (Binnion and Das Gupta, 1974; Binnion, 1975).

Although *chronic* hypokalaemia and potassium loss induced by diuretics as found in the present study are generally accepted as being able to sensitize the myocardium to the arrhythmogenic effects of digitalis in man, the available evidence for this assumption is scanty (Callahan *et al.*, 1952; Lown *et al.*, 1952; Jorgensen and Sorensen, 1970; Salvador *et al.*, 1970; Binnion, 1975; Poole-Wilson, Hall, and Cameron, 1975). Moreover, an animal experimental model, similar to the patient on chronic digitalis and diuretic therapy, has never been produced. In dogs with chronic hypokalaemia and potassium deficiency induced by dietary restriction of potassium and/or diuretics, an increased sensitivity of the myocardium to acute loads of acetyl strophanthidin or of digoxin could not be demonstrated (Kleiger *et al.*, 1965; Binnion, 1975). It may be concluded, however, that our findings are in keeping with the view that chronic hypokalaemia and potassium loss may sensitize the myocardium to digitalis in man.

In terms of electrophysiological mechanisms the appearance of cardiac arrhythmias in this setting can be explained by an increased automaticity of lower pacemakers and by a decreased atrioventricular conduction induced by digoxin in a sensitized myocardium (Surawicz and Gettes, 1971). However, the alternative possibility that the arrhythmias are induced by hypokalaemia alone must also be considered.

In the present series the degree of potassium depletion induced is reflected by the slow and gradual decrease of serum potassium of 1 mmol/l and by an overall potassium loss of 204 mmol or 11 per cent of body potassium. As shown in Tables 2 and 3 the relative loss of potassium was larger from the extracellular than from the intracellular phase, resulting in a rise in the intra-/extracellular potassium gradient for the whole body. Our findings stress the significance of hypokalaemia as a factor in the alterations in the intra-/extracellular potassium gradient, as pointed out by other authors (Surawicz and Gettes, 1971). An even larger increase is found when the myocardial intra-/extracellular potassium gradient is calculated on the assumption that the intracellular concentration of the myocardium remains unchanged during the study (Bolte, 1973; St. George *et al.*, 1955; Hall and Cameron, 1974). The electrophysiological effects of a rise in the intra-/extracellular gradient are an increased automaticity of ectopic pacemaker activity and a decreased atrioventricular conduction similar to the actions of digitalis.

In clinical experience atrial and ventricular premature beats or rhythms induced by hypokalaemia are described in patients, not on digitalis, with an incidence ranging from 20 to 40 per cent. Higher frequencies are found in patients with organic heart disease and in those given digitalis (Surawicz *et al.*, 1957; Weaver and Burchell, 1960; Davidson and Surawicz, 1967). In our series arrhythmias were observed in 50 per cent during one week of study, and a higher incidence might have been expected with a longer period of study. A comparison between the incidence in our series and in earlier reports is difficult because of the differences in the settings studied and in methods used. Consequently, the question remains undecided whether the arrhythmias are caused by hypokalaemia or are caused by a combined effect of changes in potassium balance and of digoxin.

From a clinical point of view, however, the important fact is that hypokalaemia can precipitate cardiac arrhythmias in patients receiving maintenance digoxin therapy. It is necessary, therefore, to ensure the maintenance of normal potassium balance during long-term digitalis therapy.

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