Electrocardiographic findings and frequency of arrhythmias in Bartter's syndrome

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SUMMARY Twenty four hour electrocardiograms in 20 patients with Bartter's syndrome, a disorder associated with chronic potassium deficiency, were analysed for atrial and ventricular extrasystoles, pauses (RR interval > 2 s), and heart rate. The 12 lead resting electrocardiogram was also evaluated. There were slight electrocardiographic changes with ST segment depression (≥ -0.5 mm) in seven patients, flat or low amplitude T waves in seven, and U waves ($\geq +1.0$ mm) in three patients. The QT interval was prolonged in 18 patients. Nine patients had one or more ventricular extrasystoles in 24 hours. Only two patients had more than 200 ventricular extrasystoles in 24 hours. No patient had ventricular tachycardia. A total of nine patients had one or more atrial extrasystoles in 24 hours, but only one patient had more than 200 in 24 hours. One patient had an attack of non-sustained supraventricular tachycardia. No patient had pauses.

Dangerous tachycardia was rare in these patients with chronic potassium deficiency caused by Bartter's syndrome. The general pattern of slight electrocardiographic changes may reflect an adaptation of the myocardium to hypokalaemia. Further studies are, however, needed to determine whether these findings are relevant to long term prognosis.

Potassium is responsible for most electrolyte induced disturbances of cardiac rhythm. Although several studies have shown an increase in potentially dangerous ventricular arrhythmias in patients with hypokalaemia,¹⁻³ the subject is still highly controversial.^{4,5} The cause and effect relation is obscured by inadequate study techniques and by the tendency for arrhythmia associated with the underlying diseases.

Studies with microelectrodes in rabbits showed that alterations in potassium concentrations may cause significant changes in depolarisation, repolarisation, and pacemaker activity in various cardiac cells.^{6,7} A decrease in extracellular potassium concentrations results in a more negative resting membrane potential,⁸⁻¹⁰ a prolonged action potential duration,^{8,11} and an increased slope of spontaneous diastolic depolarisation.¹¹ Theoretically, these changes could lead to increased automaticity,¹¹ slowed conduction,⁹ and/or increased dispersion of repolar-

isation and refractoriness,¹¹ which may lead to tachycardia as well as to various types of conduction disturbances.¹²⁻¹⁴ There are not many studies of the electrophysiological effects of magnesium and its interaction with potassium.¹⁵

Several studies reported a correlation between the surface electrocardiogram and changes in the action potential resulting from alterations in potassium concentrations.^{6,9} Although the surface electrocardiogram does not give precise information on the electrical behaviour of the cell, it represents the sum of all depolarisation and repolarisation of the myocardial fibres and has therefore been used to assess disturbances in electrolyte balance.

Bartter's syndrome is characterised by renal potassium wasting, hypokalaemic alkalosis, hyperreninaemia, and normal blood pressure.^{16,17} Hypomagnesaemia is also common.¹⁸ The primary defect is thought to be a renal tubular dysfunction. Bartter's syndrome is a rare hereditary disorder that is often recognised by the incidental finding of chronic hypokalaemia in an otherwise apparently healthy individual.¹⁸ The clinical significance of this chronic electrolyte disturbance is unknown. We have assessed the prevalence of atrial and ventricular

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arrhythmias and have critically evaluated the electrocardiographic changes in these patients.

Patients and methods

PATIENTS

We studied 20 patients (seven men and 13 women) in whom Bartter's syndrome was diagnosed from 1972 to 1988. The mean age at the time of the study was 44.3 years (range 24 to 69 years). All patients showed renal potassium wasting with hypokalaemia, hyperreninaemia, high or high normal urinary aldosterone excretion, and they were all normotensive. Other causes of potassium wasting—that is, renal tubular acidosis, vomiting, or abuse of diuretics—had been excluded. The plasma concentration of bicarbonate was raised or high normal, urinary chloride excretion was normal, and repeated screening for diuretics in urine was negative in all patients. No patient was taking cardioactive drugs. The long term follow up of 19 of these 20 patients has been reported elsewhere.¹⁸ Eleven patients have also been examined by bicycle ergometer stress testing and cross sectional echocardiography. Of the eleven patients who underwent an exercise test, all except one reached the predicted maximal workload and pulse rate (unpublished observations). Table 1 summarises the clinical details.

METHODS

All patients had a physical examination, a 12 lead resting electrocardiogram, and 24 hour ambulatory

Holter monitoring. Blood samples for the analysis of serum potassium, magnesium, and calcium were obtained at the time of the studies.

Electrocardiogram

The electrocardiograms were recorded on paper at a paper speed of 50 mm/s on a six channel Mingograph (Siemens Elema 82) for the analysis of PQ intervals, QRST intervals, deviations in ST segments, and amplitude of QRS complexes, T waves, and U waves. One mV corresponded to 10 mm. All measurements were made in leads II and V4. Each electrocardiogram was also interpreted according to the Minnesota code.¹⁹ The QT interval was defined as the time from QRS onset to (a) the end of the T wave (QTE) and (b) the point at which the tangent of the T wave descent crossed the baseline (QTan).²⁰ When the end of the T wave was obscured by an U wave, the T wave offset was taken as the time of intersection of the T and U wave.²¹ QT measurements were corrected for heart rate (QTc) by Bazett's formula.²² The upper limit of normal of QTc was defined as 0.425 s for men and 0.44 s for women.²² The mean value of three consecutive measurements was used in the analysis.

The electrocardiographic patterns were classified as showing changes that were "typical" of or "compatible" with hypokalaemia or "no significant changes", as described by Surawicz *et al.*²³ Classification was based on: (a) ST segment depressions ≥ 0.5 mm, (b) U wave amplitude $> +1$ mm, and (c) U wave amplitude larger than T wave amplitude in the

Table 1 Clinical and laboratory data and electrocardiographic measurements in 20 patients with Bartter's syndrome

Case No	Age (yr) and sex	Serum		PQ	QRS	QTE*		QTan*		ST		T wave		U wave	
		K (mmol/l)	Mg (mmol/l)			II	V4	II	V4	II	V4	II	V4	II	V4
1	46 F	2.8	0.5	0.18	0.11	0.46	0.42	0.44	0.41	0.5	0	3.0	2.3	0.4	0.4
2	38 F	2.3	0.5	0.15	0.09	0.45	0.45	0.46	0.43	-0.7	-0.5	2.2	2.7	0.7	0.7
3	59 F	2.4	0.5	0.18	0.07	0.45	0.45	0.45	0.48	0	0	1.2	0.8	0.3	0.3
4	27 F	3.0	0.8	0.14	0.08	0.40	0.41	0.39	0.41	0	0.5	3.7	3.2	0.7	0.7
5	44 F	2.4	0.6	0.14	0.10	0.48	0.47	0.47	0.46	-0.3	-0.4	2.5	2.8	0.6	0.7
6	38 F	2.9	0.7	0.14	0.09	0.45	0.44	0.43	0.43	-0.5	-0.4	3.0	2.5	0.5	0.4
7	24 F	2.9	0.5	0.15	0.10	0.42	0.43	0.40	0.41	0	0.5	3.5	4.8	0.1	0.2
8	66 F	2.8	0.4	0.15	0.08	—	0.49	—	0.53	-1.0	-0.5	1.0	1.3	—	—
9	43 F	3.1	0.6	0.11	0.09	0.47	0.48	0.47	0.47	-0.3	-0.2	1.5	1.5	0.4	0.3
10	40 F	3.3	0.8	0.19	0.08	0.46	0.47	0.46	0.45	0	0	2.0	2.0	0.7	0.4
11	43 F	2.3	0.7	0.17	0.12	0.49	0.48	0.46	0.44	0	0.5	4.0	4.2	0.8	0.3
12	34 F	3.0	0.7	0.15	0.11	0.47	0.47	—	—	0	0	0	—	0.3	0.5
13	34 F	2.9	0.5	0.14	0.10	0.47	0.46	0.45	0.44	-0.3	0	1.2	2.5	0.4	0.5
14	36 M	2.8	0.6	0.16	0.11	0.48	0.48	0.52	0.49	-0.5	-1.0	1.8	1.3	0.8	0.5
15	66 M	2.7	0.6	0.18	0.08	—	0.44	—	0.47	0	-0.5	0.5	0.5	0.5	0.5
16	45 M	2.4	0.6	0.16	0.10	0.42	0.41	0.45	0.43	0	0.5	2.5	3.0	1.2	1.1
17	35 M	2.7	0.6	0.19	0.09	0.62	0.62	0.52	0.53	0	0	4.5	8.0	—	—
18	54 M	2.8	0.5	0.19	0.09	0.45	0.51	0.49	0.48	0	0	3.0	4.8	1.1	1.2
19	28 M	2.4	0.5	0.14	0.09	0.45	0.43	0.48	0.42	0	0	2.0	3.3	1.0	0.8
20	69 M	2.5	0.6	0.16	0.10	0.45	0.46	0.46	0.46	0	-0.6	2.5	2.5	0.9	0.9

*Corrected for heart rate.
Normal limits of serum concentrations of potassium and magnesium at our laboratory are 3.6–4.5 mmol/l and 0.7–1.2 mmol/l respectively. Intervals are given in seconds. ST deviations and T and U wave amplitudes are given in millimetres. K, potassium; Mg, magnesium.

same lead. The electrocardiogram was classified as "typical" if three or more features were present in the two leads and as "compatible" if two features or one of the features related to the U wave were present.⁸

Holter monitoring

Ambulatory electrocardiographic recordings were obtained on two-channel 24 hour portable tape recorders (Reynolds Medilog) while the patients followed their daily activities. Each patient was asked to keep a diary of all activities during the recording. Tapes were analysed by a semiautomatic arrhythmia analyser (Reynolds Pathfinder)²⁴ operated by an experienced technician who was supervised by C B-L.

Ventricular extrasystoles were validated by the operator and analysed on printouts by C B-L. The number of false negative (missed) ventricular extrasystoles with this approach is negligible.²⁵ In three recordings with frequent ventricular extrasystoles (> 100 in 24 hours), the entire 24 hour electrocardiogram was printed out on paper and the beats counted manually. Premature normal events (that is those that occurred earlier than 30% of the preceding RR interval were defined as atrial extrasystoles) were detected on an uninterrupted replay.²⁴ This setting has been found empirically to give the best balance between the risk of missing atrial extrasystoles (false negatives) and noting false positives.²⁵ All premature normal events detected by the analyser were visually validated by the operator, who thereby minimised the number of false positive atrial extrasystoles. The electrocardiographic criteria for classification of extrasystoles were those of Friedman.²⁶ A pause was defined as an RR interval lasting > 2000 ms; compensatory pauses that followed premature QRS complexes were excluded.

We measured the mean 24 hour heart rate as the mean number of heart beats/min estimated from the total number of beats in 24 hours. The minimal heart rate was the smallest number of beats in one minute during a 24 hour period. When the normal limits for the mean 24 hour heart rate and for minimal heart rate were calculated we took into account the additive effects of age, sex, smoking, and physical activity.²⁷ The patient's participation in leisure time physical activity and their smoking habits were classified as described earlier.²⁷

STATISTICAL ANALYSIS

Values are expressed as mean (1 SD) unless otherwise stated. Pearson's coefficient of correlation was used to quantify the degree of relation between QT intervals in leads II and V4 and to assess the relation between electrocardiographic variables and serum concentrations of potassium and magnesium.

Results

No patient had a history of cardiovascular disease. Four patients reported infrequent palpitation. No patient had experienced faintness or syncope. One patient had chronic obstructive lung disease and diabetes mellitus (case 8). The physical examination was normal in all other patients.

ELECTROLYTES

The mean serum concentrations of potassium and magnesium were 2.7 (0.3) mmol/l and 0.6 (0.1) mmol/l respectively (table 1). Fifteen patients had hypomagnesaemia. The serum concentration of calcium was normal in every patient. There was no linear relation between the measured electrocardiographic variables and the serum concentrations of potassium or magnesium.

ELECTROCARDIOGRAPHIC FINDINGS

The PQ interval was normal in all patients and the mean value was 0.16 (0.02) s (table 1). Mean QRS interval was 0.09 (0.01) s; the interval was slightly prolonged in one patient (table 1).

Depression of the ST segment of ≥ 0.5 mm was found in seven patients, flat or low amplitude T waves in seven, and U wave amplitudes of ≥ 1 mm in three patients (table 1). The ST-T and U wave changes were generally slight (fig 1). By these electrocardiographic criteria seven patients had a pattern that was compatible with hypokalaemia (table 1). No patient showed a pattern that was typical of hypokalaemia on the resting electrocardiogram.

The QTE interval (onset of QRS to end of T wave) was measurable in both leads in all but two patients and the QTtan in all but three patients, in whom there was fusion with the U wave or the following P wave. All except two patients (cases 4 and 7) showed prolongation of the QTE and/or QTtan intervals (table 1). Figure 2 shows the group mean values of the QT intervals. Individual discrepancies of QT measurements between the two leads were related to the presence of superimposed U waves or delayed repolarisation changes.

HOLTER MONITORING

Nine (45%) patients had one or more ventricular extrasystoles in the 24 hour Holter recording (table 2). Two patients (cases 1 and 3) had more than 200 ventricular extrasystoles per 24 hour and one (case 7) had more than 1000. In both patients these were asymptomatic and multiform with more than two QRS configurations, and in one of them they frequently occurred in pairs and in bigeminy. Of the remaining seven patients with ventricular extrasys-

Fig 1 Mean (1 SD) ST segment deviations and T and U wave amplitudes in leads II and V4. Note the relation between the T wave amplitude and the U wave amplitude.

toles, one patient had two different QRS configurations, two had a single episode of R on T phenomenon, but none of them had pairs or episodes with bigeminy, trigeminy, or quadrigeminy. No patient had ventricular tachycardia.

Nine (45%) patients had one or more atrial extrasystoles in 24 hours, but only one patient (case 15) had more than 200 in 24 hours (table 2). One patient had a single episode of supraventricular tachycardia (case 20). The mean 24 hour heart rate was 79 (9) beats/min (range 62–90 beats/min). When corrected for age, sex, smoking habits, and physical activity the calculated mean 24 hour heart rate was higher than the predicted normal values in two patients (cases 15 and 18). In case 15 this may have been related to frequent atrial extrasystoles. The mean minimal heart rate was 56 (9) beats/min (range 41–70 beats/min). It was normal in all except two patients (cases 3 and 5), in whom it was lower than the predicted normal values. No patient had pauses (RR interval > 2.0 s).

Fig 2 Mean (1 SD) QTE and QTtan intervals in women and in men. The QT intervals are corrected for heart rate.

Discussion

Bartter's syndrome offers a unique opportunity to study clinical effects of chronic electrolyte disturbances. These patients have persistent, probably lifelong, hypokalaemia, often subnormal extracellular magnesium concentrations,¹⁸ and no apparent structural heart disease.

In most of our patients mean and minimal heart rates were normal after correction for smoking habits, age, and physical activity. In both experimental and clinical studies there is disagreement about the effect of low potassium concentration on the rate of the sinoatrial node^{9,28} but it is generally stated to depress the heart rate.²⁸

Only one patient had signs of conduction disturbances on the resting electrocardiogram or during 24 hour Holter monitoring. The PQ interval was normal in each patient and the QRS interval was also normal in all except one patient. Several experimental studies have documented a delay or block of atrioventricular conduction as the extracellular concentrations of potassium are lowered,^{9,29} and a diffuse depression of intraventricular conduction in more advanced hypokalaemia.⁹ In contrast with the high frequency

Table 2 Number of extrasystoles during 24 hour Holter monitoring in 20 patients with Bartter's syndrome

No of extrasystoles in 24 hours	VES No (%)	AES No (%)
None	11 (55)	11 (55)
≥ 1	9 (45)	9 (45)
> 10	5 (25)	3 (15)
> 100	3 (15)	2 (10)
> 200	2 (10)	1 (5)
> 1000	1 (5)	0

VES, ventricular extrasystoles; AES, atrial extrasystoles.

of conduction defects in experimentally induced hypokalaemia, prolongation of the PQ or QRS intervals has been rarely seen in clinical hypokalaemia.³⁰

In clinical hypokalaemia the most consistent electrocardiographic changes are the appearance of a prominent U wave, depression of the ST segment, and decreased amplitude of the T wave.^{8,23,30} In our patients a pattern "typical" of hypokalaemia was not seen in any individual and a pattern "compatible" with hypokalaemia was seen in only a few. These patterns were more common in patients with other diseases who had comparable serum concentrations of potassium.^{8,23} Moreover, the magnitude of the ST segment depressions and the deviations in the amplitude of T and U waves were less pronounced in our patients.³⁰

In most of our patients the QT interval was prolonged. The relation of the QT interval to the serum concentration of potassium is controversial. Some have suggested that the QT interval is prolonged by hypokalaemia³⁰ and others that it is normal or actually shortened.^{21,23} Because there are several potential sources of inaccuracy in measuring the QT intervals in the clinical setting^{31,32} it is difficult to evaluate the biological significance of minor QT changes and to use the QT interval as a reliable reflection of repolarisation changes.³³ It is, however, well known that a decrease in extracellular potassium concentrations affects repolarisation by prolonging the action potential duration.^{6,8,11}

The slight general electrocardiographic changes in our patients contrasted with those in previous studies.^{23,30} Although changes on the electrocardiogram have usually been related to abnormalities in the extracellular electrolyte concentrations, it is the altered potassium gradient across the cell membrane that induces changes on the electrocardiogram.⁸ In acute experiments, intracellular potassium concentrations are relatively stable and altered potassium gradients are largely caused by the changes in extracellular concentrations of potassium. In our patients, however, the intramyocardial potassium concentration, and thus also the gradient across the myocardial cell membrane, is unknown. There are, however, a multitude of factors (see below) that make it difficult to compare electrocardiographic and electrophysiological changes in various states of hypokalaemia.

Supraventricular and ventricular tachycardia seemed to be no more common than in healthy subjects.^{25,34} All except two of our patients had a normal 24 hour Holter recording according to the recently suggested normal limit for the number of atrial and ventricular extrasystoles in 24 hours,²⁵ that is 200 extrasystoles in 24 hours. The significance of

the single episodes of R on T phenomenon seen in two other patients with less than 200 ventricular extrasystoles in 24 hours was hard to evaluate, because most of the complex extrasystoles can occur as incidental findings in a few healthy subjects.^{25,34} In previous studies patients with hypokalaemia had more extrasystoles than a control hospital population.^{1,30} Studies with microelectrodes in rabbits showed that continued perfusion with solutions containing low concentrations of potassium leads to supraventricular and ventricular extrasystoles, ectopic tachycardia and, finally, ventricular fibrillation.⁹ The tendency for extrasystoles to develop during hypokalaemia has been attributed to several electrophysiological effects, including an enhanced automaticity, a prolonged phase 3 of the action potential duration, and an enhanced reentry caused by depressed conduction.¹²

The type of rhythm disorder induced or abolished by changes in the serum concentration of potassium depends not only on the extracellular potassium concentration but also on other factors, such as the rapidity with which the potassium concentration changes, the sensitivity of the various cardiac fibres to such changes, the extracellular concentration of other electrolytes, the underlying state of the myocardium, the interactions with neurogenic factors, and cardioactive drugs.^{8,15} Moreover, studies in rabbits showed that cardiac muscle was protected against loss of potassium during chronic potassium depletion by an adaptive increase in the density of sodium pump receptors.³⁵ It is not yet known whether these results can be extrapolated to human beings.

We found that although extracellular concentrations of potassium were usually very low in patients with Bartter's syndrome, the electrocardiographic changes were slight and arrhythmias were not common. Further studies will be needed to show whether these findings are relevant to the long term prognosis.

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