CLINICAL RESEARCH

Exercise heart rates at different serum digoxin concentrations in patients with atrial fibrillation

RICHARD BEASLEY, DENNIS A SMITH, DAVID J McHAFFIE

Abstract

Heart rate at rest and during increasing workloads was measured in a double blind study of 12 patients with chronic atrial fibrillation when serum concentrations of digoxin were nil and at low and high therapeutic values. Twelve normal subjects were studied for comparison. The heart rate at all levels of exercise in most patients with atrial fibrillation was not adequately controlled by any serum digoxin concentration tested despite a reduction in heart rate with increasing serum digoxin concentrations. Control of the resting heart rate, even in patients with high serum digoxin concentrations, did not ensure adequate control of the heart rate during work rates equivalent to regular daily activities.

Introduction

Use of digoxin in the treatment of heart failure has been debated,^{1,2} but control of the heart rate in patients with atrial fibrillation is now the least controversial and most specific indication for giving digoxin.² Digoxin usually causes slowing of the heart rate during rest, but its ability to prevent excessive increases in the heart rate during exercise is doubted.³⁻⁸ The main purpose of this study was to examine the effect of different serum digoxin concentrations on the ventricular rate at rest and during

increasing workloads in patients with atrial fibrillation, particularly a subgroup of patients with clinical criteria suggesting that they were receiving optimal treatment.

Subjects and methods

We studied 12 patients (one woman, 11 men) with atrial fibrillation. Their mean (SD) age was 48.5 (6.8) years and mean weight 86.3 (9.1) kg. All had been in atrial fibrillation for over one year and were in a stable condition. None had clinical or radiological evidence of congestive heart failure. Two patients were taking diuretics (frusemide 40 mg daily). On the basis of established criteria the aetiology of the atrial fibrillation was alcoholic heart disease in all 12 patients.⁹ Patients with clinical or echocardiographic features of rheumatic heart disease had been excluded. None of the patients had a history of angina or myocardial infarction. All were normotensive, yielded normal results to thyroid function tests, and had normal serum electrolyte (including magnesium) concentrations. Alcoholic autonomic neuropathy was excluded by clinical assessment.¹⁰

For comparison we studied 12 normal subjects (one woman, 11 men) in sinus rhythm. Their mean age was 48.1 (2.9) years and mean weight 78.7 (6.7) kg.

Patients with atrial fibrillation did three exercise tests at intervals of two weeks. The dosage of digoxin was varied in an attempt to obtain three different serum digoxin concentrations—namely, nil and low and high therapeutic concentrations. The probable range of doses to be given to each patient was determined by reference to the patient's maintenance dose and blood concentration before the trial. Placebo and active tablets (digoxin 0.125 mg) of identical appearance were used in different combinations to produce a range of doses between zero and 0.625 mg digoxin a day. One of us (RB) took no part in the exercise testing but supervised the dosages and assessed each patient for evidence of digoxin toxicity. No patient developed features suggesting toxicity, and so all took constant dose schedules for at least 10 days before each exercise test. Serum digoxin concentrations were determined by radioimmunoassay (therapeutic range 0.6–2.6 µg/l).¹¹ Those patients in atrial fibrillation with both serum digoxin concentrations above 1.6 µg/l and resting heart rates less than 90 beats/min were considered to be receiving optimal treatment and were analysed separately.

The control subjects in sinus rhythm did one exercise test.

On the day of each test heart rates were recorded on an electrocardiogram rhythm strip after the subject had rested supine for 10 minutes. Blood was then taken for measurement of serum digoxin concentration (18 hours after the last dose). The exercise test was a

Department of Medicine, Wellington Clinical School, Wellington, New Zealand

RICHARD BEASLEY, MB, CHB, Medical Research Council of New Zealand training fellow

DENNIS A SMITH, PHD, scientific officer

DAVID J McHAFFIE, FRACP, senior lecturer

Correspondence to: Dr D J McHaffie.

standard progressive load test on a treadmill.¹² Continuous recordings were made of heart rate, ventilation, consumption of oxygen, production of carbon dioxide, and respiratory quotient. To accommodate the considerable variation of heart rate seen in atrial fibrillation the heart rate was computed as a weighted average. This function minimises the beat to beat change in heart rate but registers a change within five to 10 seconds after sustained changes in heart rate.¹³ The end point of the exercise test was determined usually by the patients, who stopped the test when they considered that they could not exercise any longer. The test was stopped by the supervisor if the heart rate exceeded 220 beats/min or if the respiratory quotient exceeded 1.1.

The metabolic cost of work was measured as oxygen consumption (ml/kg/min). The adjustment for weight permits close comparison of the metabolic cost of work among individuals of various sizes.¹⁴ An oxygen consumption of 15 ml/kg/min is equivalent to walking 5 km/h on the flat.¹⁵ Exercise at low work rates was emphasised because it simulates the effort made during regular daily activities.

The study was approved by the Wellington Hospital human research ethical committee. Written informed consent was obtained from all subjects.

Results

One patient died of an unrelated accident before his final exercise test. All other patients completed the study. Compliance was confirmed by the serum digoxin concentrations. One patient continued to drink alcohol during the trial. "Nil" serum digoxin concentrations in all 12 patients were below 0.5 µg/l; the mean value of low therapeutic concentrations (n=12) was 0.8 (0.2) µg/l (range 0.6-1.3 µg/l) and of high therapeutic concentrations (n=11) 1.8 (0.7) µg/l (range 0.8-2.9 µg/l).

Table I shows that the heart rate at rest and at all levels of exercise decreased significantly with each increasing digoxin concentration (Student-Newmans Keuls test; $p < 0.05$ in all cases; $p < 0.001$ for high v low and high v nil concentrations at all levels of exercise). There was considerable variation in heart rate within the groups at each workload.

TABLE I—Mean (range) heart rate response to exercise in patients and controls

		Heart rate (beats/min) at work rates of:		
n		Rest	15 ml/kg/min	20 ml/kg/min
<i>Patients in atrial fibrillation</i>				
Digoxin concentrations:				
Nil	12	108 (82-170)	171 (128-212)	191 (145-226)
Low	12	93 (71-120)	161 (117-203)	182 (139-217)
High	11	83 (59-101)	140 (106-191)	164 (124-214)
<i>Controls in sinus rhythm</i>				
	12	72 (56-96)	105 (87-135)	118 (97-149)

TABLE II—Mean (range) heart rate response to exercise in patients considered to be receiving optimal treatment (resting heart rate < 90 beats/min and serum digoxin concentration > 1.6 µg/l) and controls

	n	Heart rate (beats/min) at work rates of:			
		Rest	15 ml/kg/min	20 ml/kg/min	25 ml/kg/min
Patients	6	79 (59-89)	135 (107-165)	162 (124-186)	184 (149-201)
Controls	12	72 (56-96)	105 (87-135)	118 (97-149)	130 (108-168)

When the patients with atrial fibrillation in whom high digoxin concentrations were achieved were compared with the controls (analysis of covariance, resting heart rate as the covariate) there was a significant difference at all levels of exercise ($p < 0.01$ at 15 ml/kg/min and $p < 0.001$ at 20 ml/kg/min). Even though their heart rate at rest was controlled, at an exercise level of 15 ml/kg/min (that is, when walking at 5 km/h on the flat) these patients had a mean heart rate of 140 beats/min compared with 105 beats/min in the controls.

The results in our controls in sinus rhythm were closely comparable with those reported elsewhere.¹⁴

Six patients with atrial fibrillation were considered, on clinical grounds, to be receiving optimal digoxin treatment. Their mean age was 49.2 (8.1) years and mean weight 87.3 (9.7) kg. All had serum digoxin concentrations greater than 1.6 µg/l (mean of 2.0 (0.4) µg/l)

and resting heart rates less than 90 beats/min (mean 79 (11.5) beats/min). Table II shows a comparison of this group with the controls. There was no difference in heart rates at rest (t test with unequal variances), but there was a significant difference at the low work rates ($p < 0.02$ at 15 ml/kg/min) and the difference increased at higher work rates ($p < 0.002$ at 20 ml/kg/min).

Discussion

The main aim of treatment with digoxin in patients with atrial fibrillation is to control the ventricular rate both at rest and during exercise.³⁻⁹ Slowing the heart rate is the most important factor as this reduces breathlessness and increases work capacity in active patients.⁵⁻⁹ Our study was designed to avoid some of the confounding variables that have influenced assessment of the control of heart rate in previous studies.³⁻⁸ Instead of comparing results from a mixed population with mitral valve and myocardial lesions we concentrated on the heart rate responses in patients with a single aetiological basis for atrial fibrillation. All patients were in a stable clinical condition and free from heart failure. Heart rate and work rate were measured directly and compared with measurements of serum digoxin concentration in a double blind protocol.

Our results show that although exercise heart rate is reduced by increasing the serum digoxin concentration, the heart rate at all levels of exercise in most patients with chronic atrial fibrillation is not adequately controlled by any therapeutic concentration of digoxin. It is common clinical practice to monitor the effects of digoxin by measuring the resting supine heart rate and the serum digoxin concentration. Our study shows that this is not a reliable guide to whether digoxin treatment is adequate because we found that in the six patients considered on these criteria to be receiving optimal treatment the heart rate was significantly increased even at low work rates.

These findings are consistent with the physiology of atrioventricular nodal conduction. The major slowing effect of digoxin on atrioventricular conduction is achieved by augmenting vagal tone.¹⁶ As vagal tone is greatest when a person is resting supine the effect of digoxin is most prominent then.¹⁷ During upright exercise much of the vagal tone (and thus the effect of digoxin) is lost, and atrioventricular conduction is further enhanced by the increased sympathetic tone, resulting in fast ventricular rates.¹⁷

If treatment with digoxin alone is insufficient several alternatives are available. After cardioversion to sinus rhythm the heart rate at rest and at all work rates is reduced and maximum effort capacity improved.⁴⁻⁶ Calcium channel blockers and β adrenergic blockers, when given in combination with digoxin, are effective in further suppressing the ventricular rate in atrial fibrillation.⁷⁻⁸ They are especially effective in decreasing the heart rate to normal values if an excessive tachycardia develops at low work rates, and their use may increase exercise tolerance.⁷⁻⁸

We conclude that, despite a reduction in heart rate with increasing serum digoxin concentrations, the heart rate at all levels of exercise in most patients with chronic atrial fibrillation is not adequately controlled by any therapeutic concentration of digoxin. Control of the resting heart rate, even in a patient with a high serum digoxin concentration, does not ensure adequate control of the heart rate at work rates equivalent to usual daily activities.

We thank Wellcome (NZ) Ltd for supplies of digoxin and placebo tablets, and Mr C Cryer for help with the statistical analysis.

References

- Guz A, McHaffie D. The use of digitalis glycosides in sinus rhythm. *Clin Sci Mol Med* 1978;55:417-21.
- Sharpe DN. Digitalis. *NZ Med J* 1983;96:288-9.
- David D, Di Segni E, Klein H, Kaplinsky E. Inefficiency of digitalis in the control of heart rate in patients with chronic atrial fibrillation: beneficial effect of an added beta adrenergic blocking agent. *Am J Cardiol* 1979;44:1379-82.
- Resnekov L. Haemodynamic studies before and after electrical conversion of atrial fibrillation and flutter to sinus rhythm. *Br Heart J* 1967;29:700-8.

- 5 Redfors A. Digoxin dosage and ventricular rate at rest and exercise in patients with atrial fibrillation. *Acta Med Scand* 1971;**190**:321-33.
- 6 McHaffie D, Smith D, O'Donnell T. Does digoxin control the heart rate on exercise in patients with atrial fibrillation? In: Oo TY, ed. *Proceedings of the sixteenth Singapore-Malaysia congress of medicine*, Singapore, 1983. Singapore: Academy of Medicine, Singapore, 1983:158-61.
- 7 Klein H, Pauzer H, De Signi E, David D, Kaplinsky E. The beneficial effects of verapamil in chronic atrial fibrillation. *Arch Intern Med* 1979;**139**:747-9.
- 8 Yahalom J, Klein H, Kaplinsky E. Beta adrenergic blockade as adjunctive oral therapy in patients with chronic atrial fibrillation. *Chest* 1977;**71**:592-6.
- 9 Sokolow M, McIlroy MB. *Clinical cardiology*. 3rd ed. Los Altos: Lange, 1981: 556-7, 642.
- 10 Duncan G, Johnson RH, Lambie DG, Whiteside EA. Evidence of vagal neuropathy in chronic alcoholics. *Lancet* 1980;ii:1053-7.
- 11 Smith TW, Butler VP, Haber E. Determination of therapeutic and toxic serum digoxin concentrations by radioimmunoassay. *N Engl J Med* 1969;**281**:1212-6.

- 12 Smith DA, O'Donnell TV. The time course during 36 weeks endurance training of changes in VO₂max and anaerobic threshold as determined with a new computerized method. *Clin Sci* 1984;**67**:229-36.
- 13 Bevington PR. *Data reduction and error analysis for the physical sciences*. New York: McGraw Hill, 1969:255-60.
- 14 Astrand P-O, Rodahl K. *Textbook of work physiology*. 2nd ed. New York: McGraw Hill, 1977:187-90, 321.
- 15 van der Walt WH, Wyndham CH. An equation for prediction of energy expenditure of walking and running. *J Appl Physiol* 1973;**34**:559-67.
- 16 Moe GK, Farah AE. Digitalis and allied cardiac glycosides. In: Goodman L, Gilman A, eds. *The pharmacological basis of therapeutics*. New York: Macmillan, 1965:674.
- 17 Rowell LB. Human cardiovascular adjustments to exercise and thermal stress. *Physiol Rev* 1974;**54**:75-159.

(Accepted 24 September 1984)

Thyroxine, methimazole, and thyroid microsomal autoantibody titres in hypothyroid Hashimoto's thyroiditis

ROLF JANSSON, ANDERS KARLSSON, PER ANDERS DAHLBERG

Abstract

Ten hypothyroid patients with Hashimoto's thyroiditis were treated with methimazole 30 mg in addition to thyroxine 0.15 mg daily. Another 10 hypothyroid patients with Hashimoto's thyroiditis were given thyroxine 0.15 mg alone. After 22 weeks of treatment significant decreases in thyroid microsomal autoantibody titres were observed in both groups ($p < 0.01$). There was no difference in the mean change in titre between the two groups. When the patients treated with methimazole were subsequently given thyroxine 0.15 mg alone for a further 22 weeks no additional change in titre was observed.

The data suggest that thyroxine, by normalising serum thyroid stimulating hormone concentrations, may reduce the autoantigenic properties of the thyrocytes with a subsequent decrease in autoantibody titres.

Introduction

Treatment of Graves' thyrotoxicosis with thionamide drugs, such as methimazole, carbimazole, and propylthiouracil, is accompanied by a decrease in thyroid autoantibody titres.¹⁻⁵ These thyrostatic drugs, which are known to be accumulated in the thyroid,⁶ have been suggested to have an immunosuppressive effect on antibody producing lymphocytes or antigen presenting monocytes located in the thyroid.^{4, 7, 8} We compared the effects of methimazole combined with thyroxine and of thyroxine alone on the titres of thyroid microsomal autoantibodies in hypothyroid patients with Hashimoto's thyroiditis. Both regimens were found to lower the antibody titres to the same extent.

Subjects and methods

Twenty patients (19 women and one man), who were referred to our outpatient thyroid clinic because of hypothyroidism, participated in the study after giving their informed consent. All patients had autoimmune goitrous thyroiditis (Hashimoto's thyroiditis), the diagnosis being based on the presence of serum thyroid microsomal autoantibodies and lymphocytic thyroiditis in fine needle aspiration biopsy specimens from the thyroid. The table shows the characteristics of the 20 patients.

The study, which was approved by the ethical committee of Uppsala University, was designed as follows (figure). Ten of the patients were treated with thyroxine and methimazole for 28 weeks (group 1). Thyroxine (Levaxin; Nyegaard, Oslo, Norway) was increased gradually by 0.05 mg every second week to a final dose of 0.15 mg. Methimazole (Thacapzol; KabiVitrum, Stockholm, Sweden) was similarly increased by 10 mg every second week to a final dose of 30 mg daily. Both drugs were given by mouth three times a day. This treatment was given for another 20 weeks and then gradually withdrawn over four weeks by 0.05 mg and 10 mg, respectively, every second week. After four weeks without treatment thyroxine alone was started again as in the initial treatment period. Another 10 patients (group 2) were given the same thyroxine treatment as group 1, but methimazole was omitted.

Blood samples were drawn zero, six, 14, 22, 30, 38, 46, and 54 weeks after the start of treatment in group 1, and thyroid function was consecutively analysed by routine radioimmunoassay methods. Similarly, blood samples were drawn zero, six, 14, 22, and 30 weeks after the start of treatment in group 2. One aliquot of serum from each sampling occasion was kept frozen at -20°C . After completion of the study all aliquots were analysed in a single assay run for the titre of thyroid microsomal autoantibodies by a commercial haemagglutination method (Thymune-M; Wellcome, Beckenham, UK). Fine needle aspiration biopsies were performed and evaluated at the department of cytology in this hospital. Serum methimazole was determined with a gas chromatographic mass spectrometric method.⁹

Student's t test for paired and unpaired data was used for statistical evaluation. The thyroid microsomal autoantibody titres were logarithmically transformed before calculations: 1:50 = 1, 1:100 = 2, 1:200 = 3, ... 1:409600 = 14.

Results

The figure shows the individual and mean thyroid microsomal autoantibody titres before and after 22 weeks of treatment in the two groups of patients. The mean thyroid microsomal autoantibody titre decreased significantly in both ($p < 0.01$ by paired t test in both groups). In both groups the microsomal autoantibody titres decreased in eight patients and remained unchanged in two. The mean decrease was similar in the two groups (NS by t test for groups).

In three patients treatment could not, for ethical reasons, be with-

Department of Internal Medicine, University Hospital, S-751 85 Uppsala, Sweden

ROLF JANSSON, MD, registrar

ANDERS KARLSSON, MD, associate professor

PER ANDERS DAHLBERG, MD, associate professor

Correspondence to: Dr R Jansson.