CLINICAL RESEARCH

Initial experience with a physiological, rate responsive pacemaker

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Abstract

A new pacemaker that can adapt the heart rate in response to the patient's metabolic requirements has been developed. This pacemaker uses the QT interval as the indicator of physiological demand. Experience in five patients showed the rate response to exercise to be smooth and progressive and to return gradually to the basic paced rate after activity stopped. Physiological rate responsive pacing resulted in a 45% increase in cardiac output when compared with fixed rate pacing. Similarly, a 57% increase in maximal exercise capacity was noted when rate responsive pacing was compared with conventional pacing at 70 beats/min.

This study showed that physiological rate responsive pacing using the QT interval provides a simple means of increasing the heart rate in accordance with the body's requirements.

Introduction

One of the main problems of long term cardiac pacing is that pacemakers are electronic devices that maintain ventricular activation at a fixed, arbitrary rate. They are therefore insensitive to the usual variability of physiological demands. This is particularly evident during exercise, when the inability to increase the pacing rate results in a limited cardiac response often insufficient to meet the increased metabolic demands.

The ideal physiological form of pacing is thus one that responds to the body's needs by varying the cardiac output. We recently described a rate responsive pacemaker that uses the QT interval as an indicator of physiological demand^{1,2} and report here our early experience with this pacing system.

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Patients

A QT sensing pacemaker was implanted in five patients (mean age 54 years) with complete, established heart block (table). Three patients were undergoing routine change of a pulse generator and had ventricular inhibited, fixed rate pacemakers and long term electrodes. The two other patients were undergoing routine implantation of a pacemaker and had short term electrodes.

The three patients with fixed rate pacemakers had restricted exercise tolerance. One had chronic rheumatic carditis and had undergone aortic valve replacement, mitral valvotomy, and permanent pacing seven years previously. A second had ischaemic heart disease, paroxysmal atrial arrhythmias, and heart block. The aetiology of the heart block in the third patient was unknown. All three patients had adequate increases in the atrial rate in response to exercise and infusion of isoprenaline.

The two patients undergoing implantation of their first pacemaker had been leading an active life before the onset of heart block and were thought likely to benefit haemodynamically from rate responsive pacing. One had atrial fibrillation in addition to complete atrio-ventricular block; the aetiology of the heart block in the other was related to an underlying congestive cardiomyopathy.

The pacemaker

We recently reported the design of this rate responsive pacemaker, which uses the QT principle, as well as our initial evaluation of the paced evoked response.^{1,2} The system uses a conventional unipolar pacing electrode with a pacemaker capable of sensing the timing of the evoked T wave that follows ventricular depolarisation. This interval between stimulus and T wave depends not only on the paced rate but also on circulating catecholamine concentrations, which provide independent physiological information.^{2,3} The pacemaker (TX1, Vitatron medical diagnostic pulse generator; Vitatron Medical BV, The Netherlands) is lithium powered and microprocessor based (RCA 1802) with a bit serial I/O that permits full transcutaneous programmability through radiofrequency coupling via a programmer head to an external microcomputer (Hewlett-Packard HP85) containing the monitor program in its operational memory. This permits analysis and programming of all conventional and T wave tracking, pacing, and sensing variables. Analysis of the amplitude of the evoked T wave (in mV) and the duration of the interval between the pacing stimulus and the peak of the T wave (in ms) may be obtained; the latter measurement permits non-invasive assessment of pharmaco-

logical and physiological events in the duration (latency) of the paced evoked response.²

Algorithms simulating normal physiological response alter the paced rate in response to relative changes in the interval between the stimulus and the T wave; a decrease in this interval causes an increase in the rate and vice versa. The sensitivity or slope of the system to the changes in the interval (from 0.5 to 5 beats/min/ms) and the slow exponential drift back to the basic rate (nulling) (from 35 to 125 beats/min/h) were programmed non-invasively soon after implantation and tailored individually to produce steady increases in rate (with a maximal rate of change set at 30 beats/min²) to reach the preset upper rate (up to 180 beats/min) over six to 12 minutes, and then gradually decrease to the basic pacing rate (60 to 70 beats/min).

In case of malfunction of the T wave tracking mode the pacemaker can revert to a standard ventricular inhibited (programmable) fixed rate mode.

Edwards Lab model No 93A 1317F) positioned in the pulmonary artery.

Holter monitoring—The patients underwent Holter monitoring over periods of 24 hours using the Oxford Medilog system. From these data a trend analysis (rate *v* time) was computed.

Statistical analysis—Student's *t* test was applied to evaluate changes in cardiac output with both forms of pacing.

Results

The results were obtained over a three month follow up period. In one patient with cardiomyopathy and low amplitude (1 mV) T waves transient loss of T wave sensing occurred on days 2-5 after the implantation of short term electrodes. There were no other sensing or pacing problems at this early follow up stage.

Maximal work load and cardiac output with fixed rate and rate responsive pacing

Age (years)	Sex	Aetiology of heart block	Maximal work load (ml oxygen uptake/min/kg/3.5)		Cardiac output (l/min)			
			Fixed rate pacing (70 beats/min)	Rate responsive pacing (maximal 125 beats/min)	Fixed rate pacing (70 beats/min)		Rate responsive pacing	
					Rest	Exercise	Rest (mean rate 66 beats/min)	Exercise (maximal 125 beats/min)
43	M	Rheumatic heart disease	6	8.5	5.2	7.2	5	14.4
62	M	Ischaemic	4.5	9	6	8.5	5.5	12.6
53	F	Unknown	4	8	6.3	8.6	5.8	11.4
48	F	Atrial fibrillation + complete heart block	7	9.5	7	13	7.2	16.3
68	M	Cardiomyopathy	5	7	4.4	9.3	4.6	13
Mean $\pm$ SD			5.3 $\pm$ 1.2	8.4 $\pm$ 0.96	5.78 $\pm$ 1	9.32 $\pm$ 2.19	5.62 $\pm$ 0.99	13.54 $\pm$ 1.87

FIG 1—Changes in length of paced ventricular cycle (ms) in response to isoprenaline 2 μ g intravenously, measured by continuous electrocardiography in lead II at standard speed (25 mm/s) and sensitivity 0.5 cm/mV.

Assessment study

Pharmacologically induced changes in rate were obtained soon after implantation of the pacemaker with administration of isoprenaline in boluses of 2 μ g intravenously. Changes in the computer assessed interval between the stimulus and the T wave were also documented, as was the timing of the rate increase from continuous recordings obtained on an HP4700A electrocardiograph.

Exercise testing—In each patient the effects of ventricular inhibited, fixed rate pacing at 70 beats/min and of rate responsive pacing (with a maximal rate set at 125 beats/min) were comparatively assessed on two separate occasions by measurements of tolerance to treadmill exercise following the Bruce protocol.⁴ Studies were performed on average two weeks after implantation of the pacemaker, and the patients were unaware of which pacing mode was being evaluated. Exercise tolerance was reported in terms of metabolic equivalents (METS) and expressed as ml oxygen uptake/min/kg/3.5.

Cardiac output was measured in triplicate both at rest and at peak exercise with both modes of pacing by the thermodilution technique (CVI model 600, Edwards Lab Model 9510A) after insertion of a Swan Ganz flow directed triple lumen catheter (CVI model 600-017,

Pharmacologically induced changes in rate—Figure 1 shows changes in the paced ventricular rate in response to isoprenaline infusion, the slope being set at 0.5 beat/min/ms. The maximal rate of 125 beats/min (cycle length 480 ms) was achieved around three and a half minutes after the infusion and then fell gradually over the next six minutes. The interval between the stimulus and the T wave assessed non-invasively at two minutes after the infusion had decreased from 340 to 320 ms.

Exercise stress testing—Figure 2 shows the smooth and progressive adaptation of ventricular rate during treadmill exercise testing with the slope programmed at 1 beat/min/ms. Increases in rate occurred within one minute of the start of the exercise; after four minutes the patient had achieved a rate of 102 beats/min and at six minutes almost 120 beats/min (paced cycle length 480 ms). Figure 3 shows this progressive decrease in the paced cycle length in the continuous electrocardiographic recordings during exercise. A gradual decline in the paced rate ensued from the eight minute period of exercise, coinciding with peak exercise work load and enabling the patient to maintain fast rates for the duration of the exercise. The ventricular rate then decreased further to resting levels (cycle length 760 ms). The exponential negative drift in the case illustrated was set at 65 beats/

min/h (fig 2). Exercise tolerance at a fixed rate (70 beats/min) and at the maximal rate response to the shortening of the interval between the stimulus and the T wave (125 beats/min) was plotted (fig 4, table). Maximal exercise capacity at the rate 70 beats/min was $5.3 \pm \text{SD } 1.2$ ml oxygen uptake/min/kg/3.5 while at the paced rate 125 beats/min it was 8.4 ± 0.96 ml oxygen uptake/min/kg/3.5 ($p < 0.01$). An almost linear relation between maximal exercise tolerance and paced heart rate was achieved.

Cardiac output—The changes in cardiac output on exercise paralleled the increased exercise tolerance (table). Mean resting cardiac output was 5.78 ± 1 l/min at fixed paced rates of 70 beats/min; on peak exercise this increased to 9.32 ± 2.19 l/min ($p < 0.01$). With rate responsive pacing resting cardiac output was similar (5.62 ± 0.99 l/min) at mean paced rates of 66 beats/min and increased with maximal exercise to 13.54 ± 1.87 l/min. The difference between resting and exercise cardiac outputs with rate responsive pacing was highly significant ($p < 0.001$); the difference between maximal cardiac output with fixed rate pacing and with rate responsive pacing was also significant ($p < 0.01$).

Holter monitoring—The fluctuations in the ventricular paced rate

FIG 2—Rate responsive pacing during treadmill exercise testing, showing smooth and progressive increase and decrease in ventricular paced rate in woman aged 53.

FIG 3—Continuous electrocardiographic recording in lead II during treadmill exercise test, showing gradual decrease in paced cycle length from 760 to 480 ms as work load increased.

during various daily activities were documented by ambulatory monitoring (fig 5); comparison with the patient's diary permitted confirmation of appropriate rate responses to exercise. The predominantly basal rate of around 80 beats/min during overnight rest is also shown.

FIG 4—Exercise work load during ventricular inhibited, fixed rate pacing at 70 beats/min (Δ) and during rate responsive pacing with peak rate of 125 beats/min ($\bullet$). Mean exercise capacity increased from 5.2 ± 0.62 to 8.5 ± 0.82 ml oxygen uptake/min/kg/3.5.

Discussion

Most standard ventricular inhibited pacemakers are set at rates fixed between 60 and 90 beats/min. The optimal rate in any person at rest, however, is not the optimal rate for exercise.

The two variables that determine cardiac output are heart rate and stroke volume. Because the heart adapts to pacing by a long term increase in the ventricular end diastolic volume and chamber size the compensation by changes in stroke volume achievable on exertion is limited. This together with the fixed paced rate ultimately benefits the cardiac output on exercise in many of these patients.

The ideal physiological form of pacing is one that responds to the body's needs for varying cardiac output. The relation between atrioventricular synchrony, cardiac contractility, heart rate, and exercise plays an important part in this. An appropriate atrial and ventricular activation sequence in patients with heart block may be achieved with atrioventricular sequential pacemakers. Although this atrioventricular synchrony may increase cardiac output by as much as 20-30% in patients with normal ventricular function,⁵ this increase by atrial systole becomes inconsequential when 200-300% increases are required by the demands of exercise. Intrinsic ventricular function,⁶ venous return, and the metabolic demands modified by exercise⁷ are also important determinants of exercise capacity in patients with pacemakers.

The most important determinant of cardiac output, however, is the intrinsic paced rate even in the absence of atrial synchrony.⁸ Appropriate changes in the ventricular paced rate may double or triple the cardiac output without changes in filling pressures, even in the absence of the atrial contribution. Furthermore, Karloff⁹ showed that at matched fast pacing rates (120 beats/min) almost identical work and cardiac output are achieved by atrioventricular sequential (atrial synchronous) and rate adjusted, non-atrioventricular sequential ventricular pacing. Knudson *et al*¹⁰ also showed that considerable increases in exercise capacity and cardiac output may be achieved by appropriately increasing the asynchronous paced ventricular rate in response to the physical activity.

The new generation of pacing devices currently under evaluation include rate responsive devices, which sense the atrium and pace the ventricle, and dual chamber automatic pacers, which pace and sense both atrium and ventricle. These

atrial synchronous pacemakers are superior to the ventricular inhibited, fixed rate pacing mode.¹¹ Some of the initial problems with these pacing devices were related to the inability of the pacemaker to differentiate between physiological and pathological tachycardias, the loss of atrial synchrony in tachycardia, the preset upper rate limits, and the incidence of pacemaker induced re-entrant atrioventricular arrhythmias¹² in patients with intact retrograde conduction.

With single chamber ventricular pacing or when sinoatrial function is abnormal alternative methods of sensing the physiological demands need to be used, that produce a physiological rate response to exercise. Two rate responsive approaches have been explored. The first uses an atrial electrographic detector,

and the variations in the QT interval in response to anti-arrhythmic drugs such as amiodarone and beta-blockers.

As in the study reported by Knudson *et al*,¹⁰ we found an almost linear relation between exercise tolerance and the peak heart rates achieved on exercise (fig 5). The mean exercise tolerance increased from 5.3 ± 1.2 ml oxygen uptake/min/kg/3.5 (with fixed rate pacing at 70 beats/min) to 8.4 ± 0.96 (at rate responsive paced rates reaching 125 beats/min). Striking symptomatic improvement was noted in the three patients who were originally restricted to low exercise levels at low fixed paced rates of 70 beats/min. These three patients all had near normal exercise tolerance at ranges that were not appreciably different from the range reported in a group of seven subjects with normal

FIG 5—Trend analysis of continuous ventricular rate as recorded by Holter monitor in patient with complete heart block and paced rate responsive rhythm, showing fluctuations in rate during various daily activities. (Note increased rate during 0700-0800, corresponding to patient's early morning exercises, and predominantly basal rate of 80 beats/min throughout night.)

which senses average atrial rate and the change in atrial rate as indicating metabolic demands. This information is then used to control the ventricular rate. There is no atrioventricular synchrony with this system (RS4/SRT pacemaker, Cardiac Pacemakers Inc). The second approach to rate responsiveness has been to use indicators of physiological demand that are independent of the atrial electrograph. Pacing systems responsive to changes in pH, oxygen tension, and respiratory rate have been designed but have not undergone successful clinical trials. We recently described the system based on QT sensing.¹² Its advantages include the use of conventional electrodes for pacing and sensing, the independence of the system from atrial activity and atrial sensing problems, and the absence of pacemaker induced re-entrant arrhythmias. Because the paced rate is not affected by fast atrial rates the maximal paced rates that can be achieved during exercise with this pacemaker are considerably higher (180 beats/min) than those achieved with atrial synchronous systems (around 130 beats/min) or asynchronous atrial sensing, rate responsive pacemakers (around 110 beats/min). Disadvantages of this T wave tracking pacemaker include those of unipolar pacing (interference), the lack of atrial synchrony,

atrioventricular conduction.¹⁰ Furthermore, the improved exercise tolerance was mimicked by a 45% increase in the mean exercise cardiac output from 9.32 ± 2.19 l/min (at 70 beats/min) to 13.54 ± 1.8 (at rates of 125 beats/min) ($p < 0.01$). This is almost within the normal relation seen between metabolic rate and cardiac output increasing on exercise in normal subjects.¹³

This initial experience confirms the possibility of obtaining a physiological response to exercise by using a pacing system dependent only on a conventional unipolar endocardial electrode and thus independent of problems of atrial activity and sensing. Physiological rate responsive pacing may result in considerable improvement in the quality of life, particularly in young people who are likely to indulge in physical activities, as evidenced by the differences in exercise tolerance and cardiac output between fixed rate and rate responsive pacing.

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Consequences of hyponatraemia and hypernatraemia in children with acute diarrhoea in Bangladesh

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Abstract

A total of 1330 children under 3 years of age who during 1979 had been admitted to the general ward of ICDDR,B Health Complex for diarrhoea with complications were studied retrospectively for the relation between types of dehydration, age, and nutritional state. Of the 1330 children, 276 (20.8%) were hyponatraemic, 969 (72.8%) isonaemic, and 85 (6.4%) hypernatraemic. The incidence of hyponatraemia increased with age, while the incidence of hypernatraemia decreased with age. There was a strong relation between types of dehydration and nutritional state. The incidence of hyponatraemia was directly related to the degree of malnutrition. The case fatality rates for types of dehydration were 10.1% in hyponatraemia, 3.8% in isonaemia, and 1.2% in hypernatraemia.

These observations suggest that hyponatraemia is a serious complication of diarrhoea in Bangladesh.

Introduction

Dehydration as a result of diarrhoea continues to be a leading cause of death in children, especially in developing countries.¹ In areas where infant malnutrition is prevalent acute gastroenteritis is common and there is a tendency towards serious complications.² Although in Western countries the various types of dehydration have been studied in small numbers, hypernatraemia is frequently recorded in diarrhoea with a higher mortality rate.³⁻⁶ The incidence of specific types of dehydration in developing countries where malnutrition is prevalent has not been well documented. Nevertheless, a few reports indicate a higher incidence of hyponatraemia, which is associated with

malnutrition.⁷⁻¹⁰ Hypernatraemia is reportedly rare in developing countries, possibly because of the high prevalence of malnutrition.^{7, 8}

We present the results of a retrospective analysis of the types of dehydration in relation to age and nutritional state of children admitted to the general ward of this hospital for diarrhoea with complications.

The ICDDR,B, formerly the Cholera Research Laboratory, is a specialised centre for research in diarrhoeal diseases in the region. The ICDDR,B Health Complex, Dacca, comprises a treatment centre, general ward, and study ward. All cases of diarrhoea with complications are admitted to the general ward for intensive medical care, while uncomplicated cases are treated in an ambulatory treatment centre. Patients for research are admitted to the study ward. The health complex treats about 100 000 cases of diarrhoea a year¹¹ in patients from the Dacca metropolitan area and beyond.

Materials and methods

During 1979 a total of 3716 patients with diarrhoea and complications were admitted to the general ward, of whom 1382 were children aged less than 3 years. Of these, 1330 children met our criteria and were accepted into the study. On admission a complete medical history was obtained from the parents of each child and a physical examination performed. Measurement of serum electrolytes, stool microscopy, and stool culture were done along with other routine laboratory examinations. Blood for electrolyte estimations was taken on admission and serum electrolytes measured on an I-L flame photometer.¹² Our biochemistry laboratory uses a quality control system of samples from the World Health Organisation.¹¹ The height and weight of the children were recorded after complete rehydration.

All the children had mild to severe dehydration and were treated intravenously with acetate solution¹³ for initial rehydration followed by either physiological saline or half strength saline plus 5% dextrose, depending on the serum sodium concentration received from the laboratory within six to eight hours. The types of dehydration were defined as hyponatraemic (serum sodium concentration < 130 mmol (mEq)/l), hypernatraemic (serum sodium concentration > 150 mmol/l), and isonaemic (serum sodium concentration 130-150 mmol/l).^{14, 15} Nutritional state of the children was assessed by the Gomez classification using weight for age.¹⁶ Bairagi¹⁷ confirmed that weight for age is a better screening test for malnutrition than weight for height. Using weight over age (expressed as a percentage) and the standards of the

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