Respiration as a reliable physiological sensor for controlling cardiac pacing rate

PAOLO ROSSI, GIANNI PLICCHI, GIANCARLO CANDUCCI, GIORGIO ROGNONI, FRANCO AINA

From the Cardiology Department, Ospedale Maggiore della Carità, Novara, Italy

SUMMARY A study was carried out to determine whether variations in the respiration rate during physical exercise could be used as a physiological variable in controlling the rate of an implanted pacemaker. The relation between respiration rate and heart rate was significantly correlated in 73 patients (19 with normal lung function, four with restrictive pulmonary disease, and 50 with obstructive airways disease) during repeated calibrated ergometric tests; no significant differences were found between the subgroups. An external computerised programmable system with algorithm control activated by a radio frequency system was used to vary the cardiac stimulation rate in relation to respiration rate in 11 patients implanted with ventricular inhibited pacemakers. In addition, a prototype programmable pacemaker dependent on respiration rate was implanted in two patients. Maximum values of oxygen uptake, minute ventilation, and work time were increased during the exercise stress tests when the variable cardiac pacing rate was used.

Thus respiration rate appears to be a valid and stable physiological variable for controlling the cardiac stimulation rate in order to improve cardiac output in patients dependent on pacemakers.

The optimal heart rate as well as the heart's energy needs are physiological variables that can change considerably from moment to moment according to neurohormonal and metabolic influences.[1] When stimulated by a conventional fixed rate pacemaker the heart no longer beats at its physiological rate. This does not, however, create a problem during moderate physical activity in patients with normal left ventricular function since the cardiac output can be adapted to the metabolic demand by an increase in stroke volume.[2]

The situation is different, however, during vigorous physical activity or in myocardial insufficiency. In these instances, particularly in myocardial insufficiency, cardiac output is heavily dependent on heart rate, since even at rest the heart has to function at its greatest possible stroke volume. An increase in cardiac output can, therefore, be obtained only by increasing the heart rate.[1] Because of these factors the atrial triggered pacemaker as well as the rate programmable pacemaker were developed.[3] Even though electrophysiological stimulation can be achieved by the former pacemaker both have presented problems during their clinical application. A possible solution

to these problems could be a pacemaker with a variable rate that adapts the rate of stimulation to the physiological needs without intervention by the patient or dependence on the sensing of atrial activity.[4-6]

In addition to adapting the stimulation rate to circulatory needs this physiological pacemaker must also obtain information on the expected performance of the heart. In theory, the information can be obtained from the sensing of any one physiological variable that continuously reflects the metabolic changes due to physical exercise, one of these variables being the respiration rate. We have studied the following aspects of this type of physiological pacemaker by (a) determining the respiration rate during physical exercise in subjects with no spontaneous disturbances of cardiac rhythm, and (b) by using an external system that varies the stimulation rate of an implanted pacemaker in accordance with changes in the respiration rate. The aims of these investigations were to determine whether variations in the respiration rate during physical exercise can be used as a physiological variable in controlling the rate of an implanted pacemaker and whether physiological variation in the stimulation rate of a ventricular inhibited pacemaker is functionally advantageous.

Patients and methods

PRELIMINARY TESTS
In the first series of tests we monitored respiratory function during repeated maximal exercise stress tests with increasing workloads using supine bicycle ergometry regulated at 50 rpm. The workload was increased by 25 W every four minutes. Reasons for stopping the stress tests were signs of fatigue, dyspnoea, or bronchial spasms when the maximum heart rate was approached. The type of test was explained to each patient, who was familiarised with the monitoring devices, so that any psychological or emotional factors adversely affecting the results of the test would be kept to a minimum.

Haemodynamic variables—During the warm up period and the exercise and recovery phases heart rate was measured for 15 seconds every minute and the respiration rate, minute ventilation, and oxygen uptake every two minutes with a 60 second sampling time. Heart rate was also monitored throughout the entire test by three thoracic electrocardiographic leads and arterial pressure determined every four minutes by auscultation. The respiration rate was determined
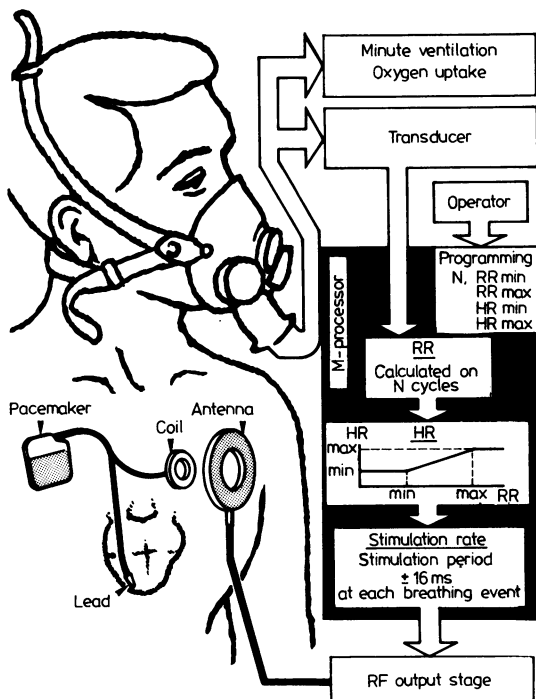

Fig. 1   *Schematic representation of external programmable system for controlling stimulation rate in response to variations in respiration rate. RF, radio frequency system; RR, respiration rate; HR, heart rate; N, respiration cycle.*

using a device attached to a rapidly responding infrared carbon dioxide sensor that continuously measured the percentage carbon dioxide. The exhaled respiratory gases were analysed with an Oxitest (Biotec) system equipped with a fuel cell type oxygen analyser and flow meter for determining oxygen uptake (standard temperature and pressure) and minute ventilation (body temperature and pressure). The patient was connected to this system by a three way rubber mouthpiece with unidirectional valves of low inertia and negligible resistance. The mouthpiece, which was fixed to the patient's face by two elastic straps, was completely air tight and connected to the cardiopulmonary analyser by a corrugated tube of sufficient diameter to minimise load losses (Fig. 1).

Subjects tested—Seventy three patients were tested (mean (SD) 48 ± 15 years) and classified according to their diagnosis and respiratory function (Table 1).

PACEMAKER STUDIES
Radio frequency system—In the second series of tests, a system was used that externally varied the stimulation rate of the implanted ventricular inhibited pacemaker. The rate was triggered by a radio frequency system consisting of (a) a radio receiver coil implanted subcutaneously at a point distant from the pulse generator site; (b) a Y shaped catheter with a unipolar endocardial lead at the proximal end and a Y shaped bifurcation at the distal end, one of the terminals being connected to the implanted pulse generator and the other to the radio receiver coil; and (c) a radio controlled pulse transmitter that could vary pulse rate and width.[7] Stimulation was achieved by placing the antenna on the skin covering the coil and activating the transmitter. A magnetic switch disrupted the implanted pulse generator so as to "connect" the radio receiver coil to the endocardial lead.

Computed respiration rate—The stimulation rate was varied by means of a computerised system that regulated the stimulation rate using the radio frequency system to maintain a constant and linear relation with the respiration rate (Fig. 1). A specific slope for the

Table 1   *Classification and diagnosis of 73 patients in relation to respiratory function*

Classification/diagnosis	No of patients	Respiratory function at rest (VEMS/VC)
Normal lung function		
Healthy and sedentary subjects	17	70–80%
Athletes (cycle riders)	2	70–80%
Chronic bronchitis and dyspnoea on effort	26	70–75%
Chronic bronchial asthma, slight pulmonary emphysema	12	60–70%
Severe pulmonary emphysema	12	50–60%
Pulmonary carcinoma	4	Within normal limits

VEMS, maximum expiratory volume/s; VC, vital capacity.

line depicting the relation between heart rate and respiration rate was selected for each patient by establishing (a) a minimum and (b) a maximum respiration rate during basal ergometric tests performed with the implanted pacemaker at a fixed heart rate; (c) a minimum heart rate of 70 beats/minute; (d) a maximum heart rate based on the theoretical rate in accordance with the subject's age or on a rate of 160 beats/minute in subjects aged 60 years. The respiration rate was measured by a sensor placed in the mouthpiece, and based on the output pulses from this sensor the rate was calculated with a "moving" average principle. The paced rate was increased by steps of two beats and related to the respiration rate expressed by the programmable relation (N) ranging from one to seven. In this way, the increments in heart rate could be obtained after one respiratory cycle (N=1) or five respiratory cycles (N=5) etc. Once the respiration rate was determined the microprocessor regulated the heart rate. The algorithm that varied the heart rate was gradual—that is, to increase from 70 to 160 beats/minute 30 respirations were required; for example, about one minute was needed if the respiration rate was equal to 30 respirations per minute. This is because for each respiration the time between two stimulation impulses could increase or decrease by only 16 ms.

Ergometric tests—These were conducted on a treadmill according to the Bruce protocol for elderly patients.[8] Cardiovascular and respiratory variables were measured using the same methods as described in the preliminary tests. The exercise tests were interrupted if muscular exhaustion or fatigue, dyspnoea, dizziness, or decreasing arterial pressure occurred. Each patient performed ergometric exercises at least twice with an interval of one hour between tests. One stress test was conducted with the implanted pacemaker at a fixed rate and the other with the paced rate varied in relation to the respiration rate according to the computerised system. During each ergometric test the moment at which the anaerobic threshold was reached was assessed. During physical exercise the ventilatory response is parallel to the workload and therefore to the oxygen uptake, until about 70% of the maximum oxygen uptake is reached. At higher workloads, a pronounced increase in minute ventilation occurs, stimulated by the production of lactic acid, and minute ventilation increases at a rate about 25 times greater than that of the increase in oxygen uptake.[9-12]

The inflection point in the line between minute ventilation and oxygen uptake was referred to in this study as the anaerobic threshold.[13] In addition, excessive minute ventilation caused by acidosis was independent of the type of exercise performed. We regarded the anaerobic threshold as our comparative reference point, since variations in heart rate could not be used as an index of comparison in our patients.

Patients studied—Eleven patients (five women and six men; age range 54–84 years, mean (SD) 69·4 ±8 years, were tested. All patients with ventricular inhibition pacemakers were connected to the radio frequency system. Each patient had a constant pacemaker rhythm and had no contraindication to the ergometric tests. Two patients (case Nos 1 and 7) were taking diuretics irregularly, one (case No 2) digitalis, and the others no medication. Four patients were classified as being in NYHA functional class I and seven in class II. The work capacity in case Nos 1, 2, 4, 6, 7, 8, 9, and 10 was determined both at a fixed stimulation rate and with the variable heart rate system one month after implantation of the pacemaker and radio frequency coil whereas in case Nos 3, 5, and 11 the patients were stress tested at seven days after implantation. In case Nos 3 and 5 the stress tests were repeated one month after implantation, since in the first exercise test the anaerobic threshold was not attained.

Results

PRELIMINARY TESTS
To assess the existing relation between oxygen uptake, heart rate, and respiration rate, the statistical calculation of the regression line and correlation coefficient for (a) oxygen uptake and heart rate; (b) oxygen uptake and respiration rate; and (c) heart rate and respiration rate was made. The correlation coefficients (r) for the above paired variables were 0·83±0·10; 0·70±0·15; and 0·76±0·14 respectively. Owing to the scatter it was not possible to determine any correlation between the total number of variables and the total number of cases. There was a closer more significant correlation coefficient between the variables when analysed for individual patients.

When grouped according to diagnosis the patients did not show any statistically significant differences. The degree of correlation reported was, therefore, not linked to the type of disorder.

These results indicate that (a) the relation between oxygen uptake and heart rate is characterised by an r value of 0·83±0·1, confirming the close correlation between heart rate and work performed by subjects without rhythm or conduction defects; (b) the relation between oxygen uptake and respiration rate is characterised by an r value of 0·76±0·14, thus depicting a good correlation between these two variables and showing that respiration rate is also an indicator of the work performed in an individual patient and an easy and reliable variable to measure; and (c) the relation between heart rate and respiration rate is characterised by an r value of 0·70±0·15, a lesser degree of
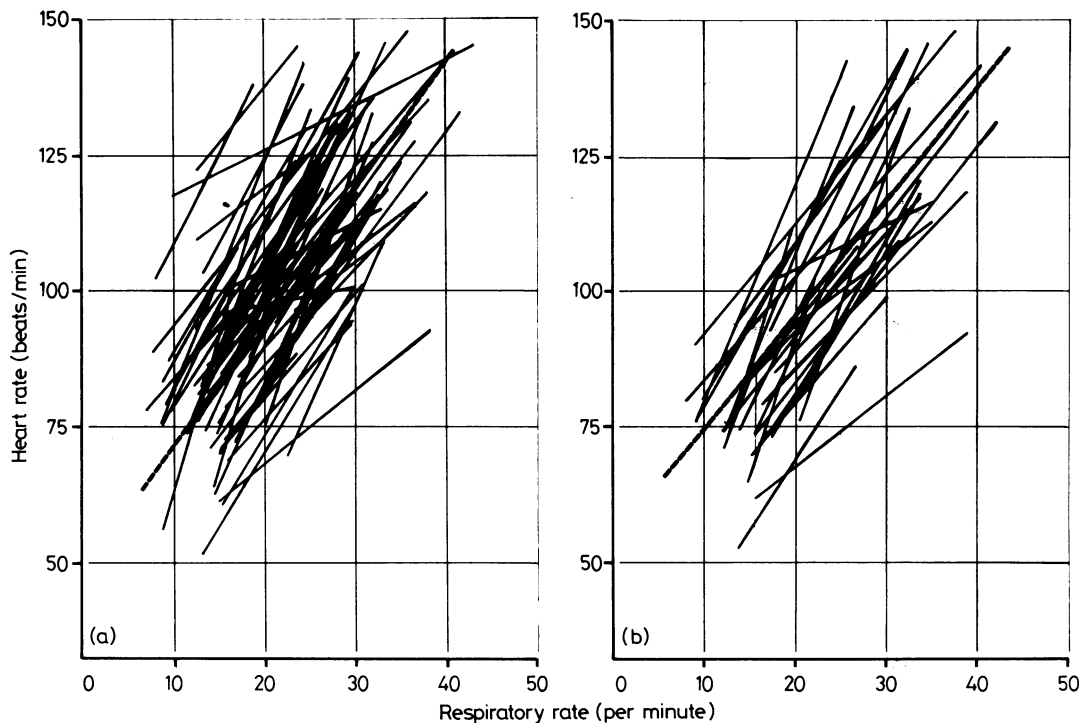
Fig. 2 *Selected individual regression lines between respiration rate and heart rate. Dotted line denotes the regression line of the mean.*
(a) Significant at p<0·05, and (b) significant at p<0·001.

correlation than with the other paired variables.

In 86% of cases the correlation coefficient between heart rate and respiration rate was significant (p<0·05) and in 42% of the cases p<0·001. Fig. 2 shows the regression line (defined by the minimum and maximum heart rate and respiration rate) obtained by correlating respiration rate and heart rate in patients in whom p was <0·05 and <0·001 respectively. As can be seen, there is a group of regression lines that are more concentrated inside the area defined by heart rates of 75–130 beats/minute and respiration rates of 15–30 respirations/minute.

PACEMAKER STUDIES
The results of the exercise tests using a fixed stimulation rate were used as controls. Each control test was compared with the test performed with an increasing stimulation rate and the following variables were analysed: work time, oxygen uptake at rest, oxygen uptake, minute ventilation, respiration rate, and heart rate. The observed data were then statistically analysed with Student's t test for paired data. The results are shown in Table 2.

A comparison between the ergometric test with a fixed heart rate and the test with a variable heart rate

is reliable, since all patients exercised until they reached the anaerobic threshold. Fig. 3(a) shows that in the tests using the fixed paced rate all patients had a sudden increase in minute ventilation at a specific point in relation to oxygen uptake. In the stress tests with the variable heart rate system (Fig. 3(b)), the anaerobic threshold point was either shifted toward the right or not attained with corresponding increases in oxygen uptake. In these tests all patients, with the exception of one (case No. 7) increased the duration of physical exercise and increased their maximum oxygen uptake. The mean (±SD) duration of exercise or work time with the fixed rate was 9·36±2·56 minutes whereas that with the variable heart rate system was 12±2·8 minutes (p<0·001).

The maximum minute ventilation increased with the variable heart rate system in seven patients, while maximum respiration rate was greater during the second exercise test in six patients. The recovery time decreased in the second test for five patients but did not vary in the other patients who showed an increase in work time. The paced rate, as regulated by respiration rate, did not attain the theoretical maximum heart rate in six cases, in one of which (case No. 7) the work time decreased in the second exercise test prob-

Table 2 *Haemodynamic and respiratory variables during exercise stress tests in 11 patients with ventricular inhibited pacemakers (A) with fixed stimulation rate (70 beats/minute) and (B) with stimulation rate controlled*

Case No	Sex	Age (years)	Cardiac volume (ml/m²)*	Functional class (NYHA)	Effort time (min)		VO₂ max (ml/min)		VE max (l/min)		RR max (N/min)		MET (O₂/kg/min)		Recovery (min)		FC max	
					A	B	A	B	A	B	A	B	A	B	A	B	T	R
1	F	71	396	II	12	14·5	720	870	38	35	36	40	3·7	4·5	7'	3'	149	150
2	M	74	640	II	9	13	1156	1455	34	49	26	26	4·6	5·5	7'	4'	142	114
3	F	71	550	II	8	9·5	580	602	30	25·7	41	41	3	3·2	6'	6'	149	140
4	M	53	410	I	6	11	1200	1600	50	65	33	38	5	6·7	6'	4'	167	147
5	M	60	670	II	5	6	765	851	59	51	48	41	3·9	4·4	3'	2'	160	144
6	M	71	670	II	8·5	11·5	1340	1750	48	73	28	37	4·3	6·1	6'	6'	149	120
7	M	69	1190	II	11·5	10	1520	1450	56	48	50	37	4·1	3·9	5'	4'	151	118
8	F	84	450	II	8·5	12·5	600	730	26	32	28	33	2·8	3·5	6'	6'	186	134
9	M	65	410	I	9·5	13·5	1280	1700	41	62	23	27	5·8	7·2	4'	4'	156	156
10	F	68	390	I	13	16·5	819	959	35	37	40	38	3·1	4·5	4'	4'	150	150
11	F	75	400	I	12	14	665	775	32	34	32	34	3·3	3·7	3'	3'	148	147
Mean		69			9·36	12	967	1158	40·8	46·5	35	35·6	3·9	4·8	5·18	4·8		
±SD		±8			± 2·5	± 28	± 336	± 443	± 10·9	± 15·3	± 8·9	± 5·1	± 0·92	± 1·3	± 1·47	± 1·32		
Probability					p<0·001		p<0·005		NS		NS		p<0·005		p<0·05			

*Cardiac volume measured from the thoracic x ray using geometric ellipsoid method.[15]
VO₂ max, maximum oxygen uptake; VE max, maximum minute ventilation; RR max, maximum respiration rate (cycles/min); FC max; maximum cardiac stimulation rate (T, theoretical (220−age); R during test); MET, oxygen uptake at rest.

ably owing to latent cardiac decompensation. In the other four cases this may have resulted from a fault in the programming of the system.

The maximum respiration rate was not the same in the two stress tests and in three cases the respiration rate was higher than during those tests performed with the variable heart rate system. The mean respiration rates during physical exercise with the fixed and variable heart rate systems were similar. The most gradual and limited increase in respiration rate after the onset of exercise tests with regulated respiration rate pacing was not significantly different from those with fixed pacing at a lower rate and can be related to the fact that some patients did not attain their anaerobic threshold, even though the work and oxygen uptake increased (Fig. 3). Fig. 4 shows the oxygen uptake, heart rate, and respiration rate during an ergometric stress test in one patient in more detail.

Discussion

Of the physiological variables with potential theoretical application in controlling the stimulation rate for a physiological pacemaker, we considered those originating from the heart or directly reflecting metabolism to be unreliable. Variables associated with cardiac function such as the P wave or the QT interval are frequently altered in patients with pacemakers because of sick sinus syndrome, atrial tachyarrhythmias, electrolytic imbalances, or pharmacological effects. The metabolic variables such as pH, central blood temperature, or oxygen pressure may present technical difficulties when used as sensors with an implanted pacemaker or they may not be sensitive enough.

We, therefore, directed our attention to respiratory variables, of which respiration rate seemed to be the most appropriate for use. The first problem to be resolved was that of defining the existing relation between respiration rate and the heart rate during physical exercise in healthy subjects and in subjects without chronotropic cardiac dysfunction or neurological diseases that preclude the use of calibrated ergometric stress tests.

The mathematical analysis of the data from the 73 subjects showed a highly significant linear relation between respiration rate and heart rate, but the regression line indicated various distances from line zero and different slopes from subject to subject. At first this appeared to rule out any single generalised solution. It was, therefore, necessary to design a programmable algorithm so that minimum and maximum values and the slope of the curve of each individual subject could be selected. The algorithm proved to be reliable because the heart rate, when controlled by the respiration rate, increased progressively during the calibrated stress test and provided a parallel trend to oxygen uptake during exercise as well as during recovery, as shown in Fig. 4.

The second problem was to show that a pacing system regulated by respiration rate would be useful in patients with a ventricular inhibited pacemaker. In a previous report, we found that the radio frequency system, as used for chronic myocardial threshold measurements,[7] could produce gradual increases in the stimulation rate during physical exercise in patients with pacemakers, thus resulting in increased work capacity.[14] Such an improvement was observed in patients without myocardial insufficiency. Our system varied the ventricular stimulation rate without
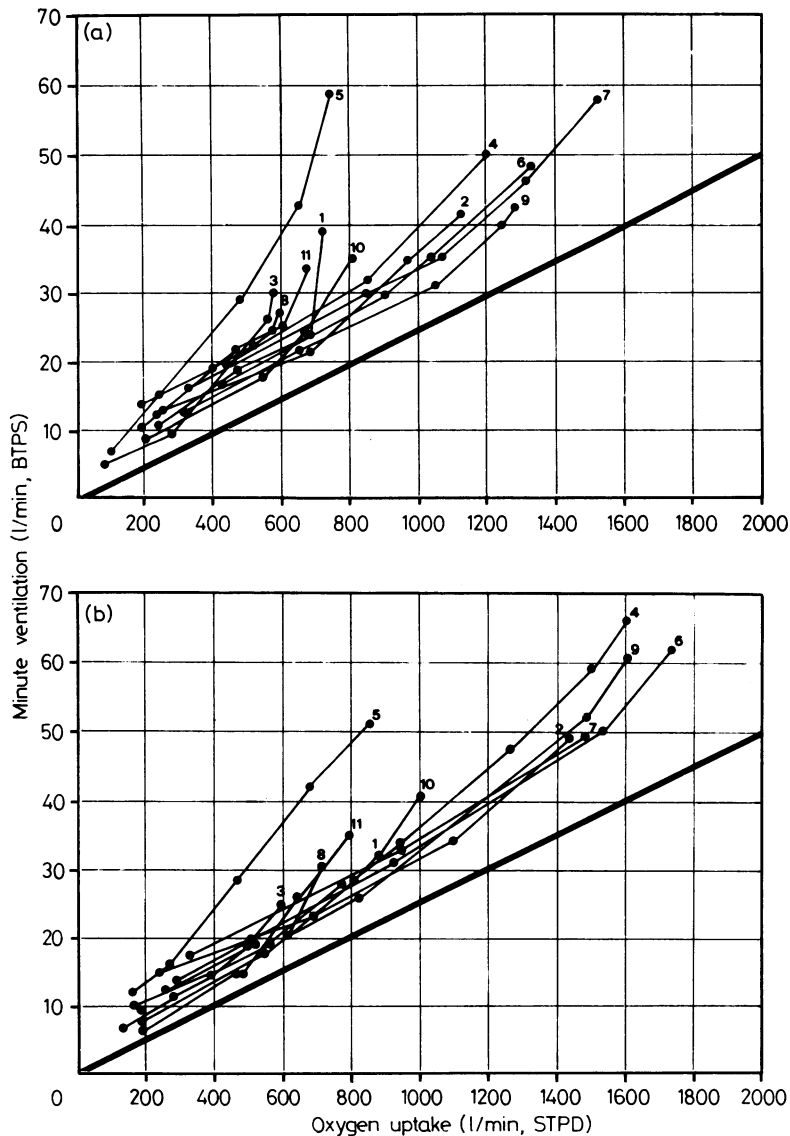
Fig. 3 *Results of exercise stress test (a) with fixed heart rate (minute ventilation compared with oxygen uptake) (note the pronounced increase in minute ventilation with increasing oxygen uptake for each patient at their anaerobic threshold point) and (b) with variable heart rate (minute ventilation compared with oxygen uptake) (note that anaerobic threshold point for most patients has shifted to the right or occurs at high values for oxygen uptake).*

constantly maintaining atrioventricular synchrony. These results, therefore, suggested that continuous atrioventricular synchrony may not be necessary for physiological pacing. In addition, the radio frequency system was found to be useful when experimenting with the algorithm to correlate respiration rate with the heart rate.

Our results showed that physical work capacity improved in all subjects without myocardial insufficiency when the stimulation rate was controlled by the respiration rate. The significant increase in work

capacity observed during exercise using the variable cardiac rate system confirmed our earlier results. A significant increase in maximum oxygen uptake and oxygen uptake at rest was confirmed in these subjects.

In the second series of tests it was interesting to note that although the work time was extended the recovery period was shorter than that during the first exercise tests. Nevertheless, an improvement in work capacity was shown. Psychological or emotional factors, especially in older patients, can be important in influencing the results of the exercise tests, thus mak-
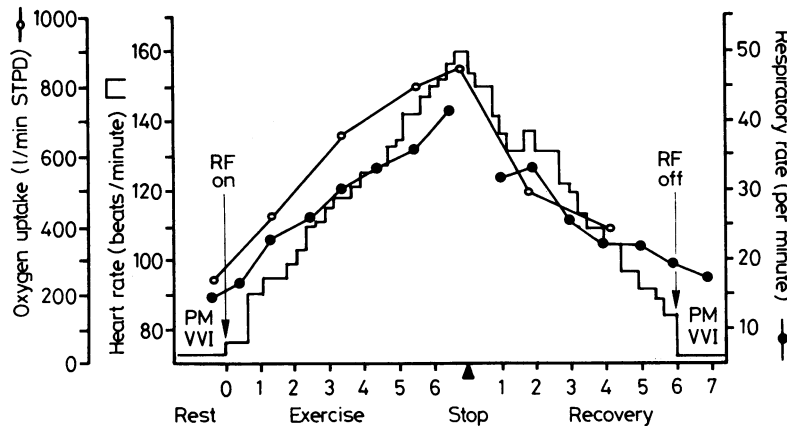
Fig. 4 *Haemodynamic and respiratory variables in a patient with complete atrioventricular block fitted with a ventricular inhibited pacemaker (VVI). Variable cardiac stimulation rate was controlled by radio frequency (RF) system in response to respiration rate.*

ing the comparison between two tests conducted at different times difficult. Since our patients exercised until they reached their anaerobic threshold, we can exclude the influence of any psychological or emotional factors. In our previous studies patients with ventricular inhibition pacemakers were invariably able to perform two or three exercise tests at a fixed stimulation rate. The anaerobic threshold was attained at the same workload excluding a warming up effect of double exercise testing.

The analysis of individual cases shows particular variations in results which deserve attention. Even though the mean respiration rate was noticeably constant in the first as well as in the second series of stress tests, the maximum respiration rate during the ergometric test with a fixed heart rate was in some cases lower than that during ergometric tests with a variable heart rate. The programming of the algorithm could, therefore, be improved only after the second exercise test. Certain patients did not attain their theoretical maximum heart rate, probably because of latent cardiac insufficiency (case No 7) or faulty algorithm programming (case Nos 2, 4, 5, and 6). In all cases controlled stimulation resulted in definite functional improvement. In addition, the relation between respiration rate and oxygen uptake was excellent and independent of age.

In conclusion, the increased venous flow produced by muscular activity provides adequate ventricular filling even when atrioventricular synchrony is absent. An increase in the stimulation rate during physical activity, even if applied to the ventricles only, can, therefore, produce haemodynamic improvement. The respiration rate seems to be a valid and stable physiological variable by which to control the cardiac stimulation rate in order to obtain an improved exercise tolerance in subjects whose cardiac rhythm depends on a pacemaker. Our results show that an external programmable system can be used with

physiological pacemakers, since the ventricular rate sensor and algorithm for correlating respiration rate and heart rate can be programmed into an implantable pacemaker. In our device the breathing rate was monitored by impedance variation in the respiration, detected between the pacemaker casing and a lead placed in the subcutaneous layer of the thoracic region. Programmable pacemakers based on respiration rate were implanted in two patients and at seven and 11 months after implantation are functioning satisfactorily.

References

1 Epstein SE, Beiser GD, Stampfer M, Robinson BF, Braunwald E. Characterization of the circulatory response to maximal upright exercise in normal subjects and patients with heart disease. *Circulation* 1967; **35:** 1049–62.
2 Sowton E. Haemodynamic studies in patients with artificial pacemakers. *Br Heart J* 1967; **26:** 737–46.
3 Nathan DA, Center S, Wu CY, Keller W. An implantable synchronous pacemaker for the long term correction of complete heart block. *Am J Cardiol* 1963; **11:** 362–7.
4 Cammilli L, Green GD, Ricci D, Risani R. pH-triggered pacemaker: Design and clinical results. In: Meere C, ed. *Cardiac pacing. Proceedings of the VIth World Symposium on cardiac pacing.* Ch. 19–8. Quebec, Montreal: International Cardiac Pacing Society, 1979.
5 Ionescu VL. An "on demand pacemaker" responsive to respiration rate [Abstract]. *PACE* 1980; **3:** 375.
6 Rickards AF, Norman J. Relation between QT interval and heart rate. New design of physiologically adaptive cardiac pacemaker. *Br Heart J* 1981; **45:** 56–61.
7 Rossi P, Palma G, Marino B, De Bellis F, Solina A, Vercellotti F. Long term follow-up of myocardial pacing threshold measurement with an external radiofrequency transmitter in patients with an implanted pacemaker and an independent radio receiver (Radiocor). In: Watanabe

Y, ed. *Cardiac pacing. Proceedings of the Vth International Symposium.* Amsterdam & Oxford: Excerpta Medica, 1977: 433–7.

8 Bruce RA. Exercise testing of patients with coronary artery disease. *Ann Clin Res* 1971; **3**: 323–32.

9 Asmussen E. Muscular exercise. In: *Handbook of physiology and respiration.* Washington, DC: American Physiological Society 2, 1965: 939–78.

10 Astrand I. Aerobic work capacity in men and women with special references to age. *Acta Physiol Scand* 1960; (suppl 169): 15.

11 Astrand PO, Saltin B. Maximal oxygen uptake and heart rate in various types of muscular activity. *J Appl Physiol* 1961; **16**: 977–81.

12 Brouha L, Radford EP Jr. The cardiovascular system in muscular activity. In: Johnson W, ed. *Science and medicine of exercise and sports.* New York: Harper, 1960: 178–206.

13 Koyal SN, Whipp BJ, Huntsman D, Bray GA, Wasserman K. Ventilatory responses to the metabolic acidosis of treadmill and cycle ergometry. *J Appl Physiol* 1976; **40**: 864–7.

14 Rossi P, Rognoni G, Occhetta E, Aina F. Une nouvelle approche d'adaption du rythme cardiaque aux imperatifs metaboliques des patients stimulo-dependants. In: Mugica J, ed. *Les années 80 de la stimulation cardiaque. Proceedings of the Cardiostim 80.* Paris: SEPFI, 1980: 49–54.

15 Musshoff K. Die Methoden der röntgenologischen Herzvolumenbestimmung und ihre Fehlerbreite. *Fortschr Geb RöntgStrahl* 1964; **100**: 165–80.