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Extrapolated maximal oxygen consumption: a new method for the objective analysis of respiratory gas exchange during exercise

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SUMMARY Respiratory gas exchange was measured during maximal treadmill exercise testing in six healthy volunteers and 20 patients with chronic heart failure. A curve of equation $y = ax - bx^2$ was used to model the relation between the rate of oxygen consumption (y axis) and the rate of carbon dioxide production (x axis). The constants "a" and "b" were used to calculate the maximal value of the expression $ax - bx^2$. This value was termed the "extrapolated maximal oxygen consumption". For all subjects a close fit between experimental data and mathematical model was obtained and the values of the measured maximal rate of oxygen consumption and "extrapolated maximal oxygen consumption" were similar. Respiratory gas exchange was reanalysed using only those values obtained during the first 90%, 75%, and 66% of exercise. In contrast with the value for the measured rate of oxygen consumption, the value of "extrapolated maximal oxygen consumption" was effectively independent of exercise duration.

Extrapolated maximal oxygen consumption provides an objective measure of cardiorespiratory functional reserve that, within limits, is independent of exercise duration. Extrapolated maximal oxygen consumption is complementary to the direct measurement of the maximal rate of oxygen consumption and increases the amount of information derived from a single exercise test.

An important problem in the assessment of patients with chronic heart failure is the lack of an objective and effort independent measure of cardiorespiratory functional reserve.[1] In recent years there has been renewed interest in the measurement of the maximum rate of oxygen consumption ($\dot{V}O_2$ max) and anaerobic threshold,[2-4] but both of these measurements have limitations.

Early studies of respiratory gas exchange in patients with chronic heart failure reported that the rate of oxygen consumption ($\dot{V}O_2$) during treadmill exercise reached a plateau before the patient reached maximal workload.[5] This plateau was believed to represent the combination of maximum cardiac output and maximum oxygen extraction by the tissues. Accordingly measurement of $\dot{V}O_2$ max was claimed to provide an objective measure of cardiovascular function. In our experience,[4] and in that of many other laboratories,[1] it is rare to see a true plateau in oxygen consumption during treadmill exercise. Measured $\dot{V}O_2$ max is therefore effort dependent and may be altered by changes in patient motivation or supervisor encouragement. In consequence, $\dot{V}O_2$ max is essentially a symptom limited measurement of exercise tolerance and, as such, will reflect not only cardiorespiratory functional reserve but also the individual's perception and tolerance of symptoms.

The supply of energy to working skeletal muscle by anaerobic metabolism increases with workload. The mechanisms responsible for this transition are complex,[6] but are at least in part caused by inadequate blood supply to active muscle.[6-8] Anaerobic metabolism produces lactic acid which is buffered by bicarbonate with the consequent liberation of carbon dioxide. Thus the rate of carbon dioxide production ($\dot{V}CO_2$) rises disproportionately to $\dot{V}O_2$. The definition of the anaerobic threshold is an attempt to attribute the onset of anaerobic metabolism to a specific point during exercise.[7] Most commonly anaerobic threshold is determined subjectively as the

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supposed point during exercise at which the relation between $\dot{V}CO_2$ and $\dot{V}O_2$ departs from linearity.[9 10] This form of analysis is unsatisfactory on two counts—first because it is subjective and secondly because there is a range of anaerobic metabolism that alters in rate rather than starting and stopping at a fixed workload.

In an attempt to obtain an objective measurement of cardiorespiratory functional reserve that is independent of exercise duration we have developed a new method for the analysis of respiratory gas exchange during exercise. Our method resembles that used to determine anaerobic threshold in that it uses the non-linear relation between $\dot{V}O_2$ and $\dot{V}CO_2$ that occurs with increasing workload. In contrast with anaerobic threshold our method does not attempt to attribute the onset of anaerobic metabolism to a fixed point during exercise. Instead the relation between $\dot{V}O_2$ and $\dot{V}CO_2$ is analysed by means of curve fitting. The curve is then extrapolated mathematically to determine the theoretical maximal value that oxygen consumption can attain. We have named this measurement the "extrapolated maximum oxygen consumption". We describe the method and compare its results with those of the conventional measurement of $\dot{V}O_2$ max.

Patients and methods

We studied six healthy volunteers and 20 patients with chronic stable heart failure. Table 1 shows age, sex, diagnosis, and $\dot{V}O_2$ max of each subject. All subjects were selected because of their ability to perform maximal symptom limited, treadmill exercise testing that fulfilled the following criteria. Exercise was limited by fatigue or shortness of breath or both. Patients exercised for at least four minutes. The respiratory exchange ratio rose progressively during exercise, reaching a value >1 for at least the last 30 seconds of exercise. The last criterion was used to ensure that a level of exercise had been achieved that stressed cardiovascular function.[11]

Patients with myocardial infarction during the preceding three months, evidence of myocardial ischaemia or ventricular arrythmias during exercise, obstructive valvar heart disease, hypertrophic cardiomyopathy, or appreciable pulmonary disease (documented by lung function tests) were excluded from the study.

EXERCISE TEST

Exercise tests were performed by the modified Bruce protocol, in an air conditioned laboratory, with room

Table 1 *Individual results for the full duration of exercise for $\dot{V}O_2$ max (measured maximal rate of oxygen consumption), r (correlation coefficient for curve fitting), and extrapolated maximal oxygen consumption (EMOC)*

Subject	*Age*	*Sex*	*Diagnosis*	*$\dot{V}O_2$ max*	*r*	*EMOC*	*$\dot{V}O_2$* max/EMOC%
1	25	M	Normal	49·4	−0·94	52·2	94·7
2	33	F	Normal	39·8	−0·94	44·7	89·0
3	30	M	Normal	37·1	−0·94	36·1	102·8
4	29	F	Normal	33·7	−0·93	34·9	96·9
5	29	M	Normal	33·6	−0·94	36·8	91·4
6	27	F	Normal	26·8	−0·97	27·1	98·0
7	60	M	AVR	24·7	−0·94	24·7	99·9
8	53	M	IHD	23·1	−0·94	22·9	100·8
9	32	M	IHD	22·6	−0·93	24·2	93·0
10	57	M	MR	21·3	−0·89	23·6	90·6
11	29	F	COCM	21·3	−0·98	20·9	102·0
12	45	M	Sarcoid	20·0	−0·95	19·9	100·5
13	50	M	IHD	19·1	−0·96	19·9	96·0
14	57	M	COCM	18·4	−0·97	18·9	97·4
15	57	M	COCM	16·5	−0·92	17·3	95·4
16	65	M	AVR	14·7	−0·86	15·1	97·3
17	41	M	COCM	14·6	−0·85	17·2	85·1
18	50	M	IHD	13·7	−0·86	14·5	94·4
19	29	F	COCM	13·4	−0·89	13·9	96·2
20	51	M	COCM	13·1	−0·79	12·7	102·7
21	54	F	IHD	12·8	−0·79	14·3	90·0
22	44	M	AVR	12·7	−0·96	13·3	95·3
23	59	F	IHD	12·6	−0·93	14·6	86·6
24	53	M	IHD	12·0	−0·73	12·7	94·5
25	56	M	IHD	9·7	−0·88	9·9	98·1
26	49	M	IHD	9·6	−0·90	10·1	95·8
Maximum	65	—	—	49·4	−0·73	52·2	102·8
Minimum	25	—	—	9·6	−0·98	9·9	85·1
Mean	—	—	—	—	−0·91	—	95·6
SD	—	—	—	—	0·06	—	4·7

AVR, after aortic valve replacement; IHD, ischaemic heart disease; MR, mitral reflux; COCM, congestive cardiomyopathy.

temperature maintained in the range 20–21°C. All subjects had been previously familiarised with treadmill exercise and measurement of respiratory gas exchange. Patients continued their normal medication on the day of exercise tests and all tests were performed at least three hours after meals.

Minute ventilation (VE), $\dot{V}O_2$, and $\dot{V}CO_2$ were measured continuously by the method of Davies and Dennison.[12] Validation and reproducibility of this method in our laboratory has already been described.[4] In brief, subjects were required to breathe through a two way respiratory valve (Collins) held by an adjustable head support. The expiratory port was connected, via flexible tubing, to a 7 litre mixing box (Airspec). Argon was added to the inlet port of the mixing box at a constant flow rate. After full mixing, the resulting gas mixture was continuously analysed by a mass spectrometer (Airspec 200 MGE). The analogue output from the mass spectrometer was fed to the analogue to digital input channels of a microcomputer (BBC model B). Analogue to digital conversions were performed every 200 ms for each of the four channels (nitrogen, oxygen, carbon dioxide, and argon). Every 10 s, a mean value for each channel was calculated, and from these mean values of minute ventilation, $\dot{V}O_2$, $\dot{V}CO_2$, and respiratory exchange ratio were calculated. Values were corrected for atmospheric pressure, laboratory temperature, water vapour pressure, and body weight so as to give the following dimensions: $\dot{V}O_2$ and $\dot{V}CO_2$ in ml/kg/min at standard temperature and pressure (dry); minute ventilation as l/min at body temperature, pressure (prevailing atmospheric), and saturation (water vapour); and the respiratory exchange ratio.

DATA ANALYSIS

$\dot{V}O_2$ max was defined as the maximal mean value of $\dot{V}O_2$ over a 30 second period. The relation between $\dot{V}O_2$ and $\dot{V}CO_2$ was analysed by curve fitting. The mathematical model that was used is given by the equation $y = ax - bx^2$ where x and y represent $\dot{V}CO_2$ and $\dot{V}O_2$ respectively. The equation describes a curve with two components (fig 1). Firstly, a linear component, given by the equation $y = ax$, that passes through the origin and has a slope determined by the constant "a". The value of "a" represents the ratio of $\dot{V}O_2$ to $\dot{V}CO_2$ at the start of exercise (the reciprocal of the resting respiratory quotient). Secondly, a nonlinear component, given by the equation $y = bx^2$, the rate of rise of this expression being determined by the value of the constant "b". By subtracting the second component from the first a progressive deviation from linearity was obtained. The rate of deviation from linearity, determined by the value of "b", was used to model the disproportionate increase in $\dot{V}CO_2$ relative to $\dot{V}O_2$ that occurred with increasing workload.

For each set of $\dot{V}O_2/\dot{V}CO_2$ data the values of "a" and "b" that provided the "best fit" curve were determined. The method (fig 2) used a linear transformation followed by least squares linear regression. The correlation coefficient (r) provided a measure of the accuracy of fit between the mathematical model and the raw data.

Once determined, the values of "a" and "b" were used to calculate the maximal value that the equation $y = ax - bx^2$ could attain. The calculation was in effect an extrapolation of the fitted curve to its maximum value. This value was named the extrapolated maximum oxygen consumption. The mathematical derivation of extrapolated maximal oxygen consumption is shown below:

$$y = ax - bx^2 \quad (1)$$
$$dy/dx = a - 2bx \quad (2)$$
$$dy/dx = 0 \text{ when } x = a/2b \quad (3)$$

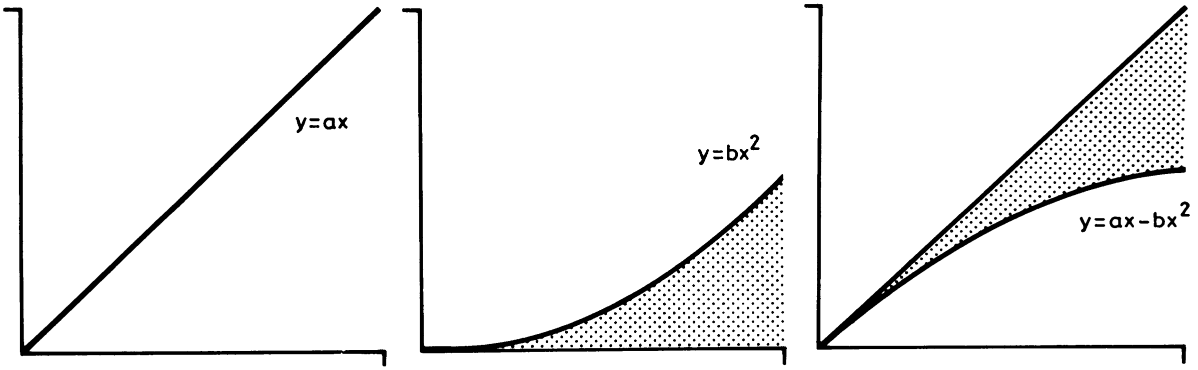

Fig 1 *Illustration of the two components of the equation* $y = ax - bx^2$ *(see text for explanation).*

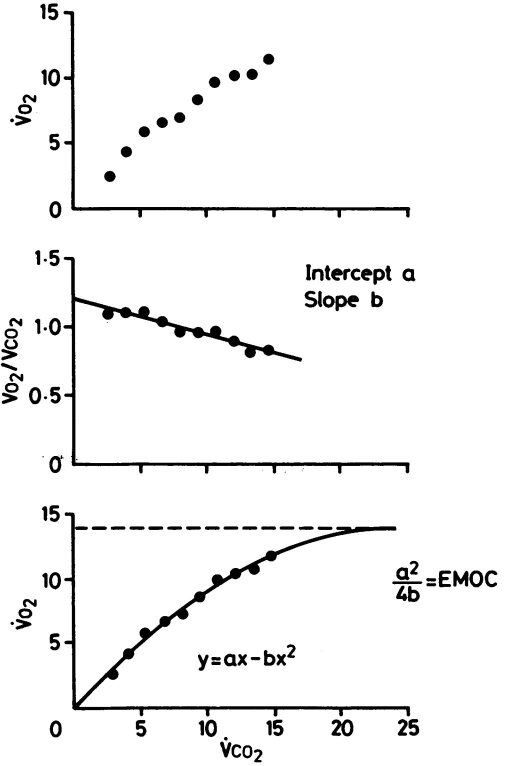

Fig 2 *Method used for curve fitting. The upper graph is a set of raw data for oxygen consumption ($\dot{V}O_2$) and carbon dioxide production ($\dot{V}CO_2$) during a single exercise test. The middle graph shows the linear transformation and least squares linear regression analysis used to determine the values of the constants "a" and "b". The lower graph shows the fitted curve and the derivation of extrapolated maximal oxygen consumption (EMOC).*

substituting (3) into (1)
$y = a^2/2b - ba^2/4b^2$
which simplifies to $y = a^2/4b$

therefore extrapolated maximal oxygen consumption = $a^2/4b$.

In order to investigate the relative dependence of extrapolated maximal oxygen consumption and $\dot{V}O_2$ on exercise duration, data from each subject were reanalysed using only those values obtained during the first 90% of exercise duration, the first 75% of exercise duration, and the first 66% of exercise duration. During each reanalysis, the methodology used was identical to that used for analysis of the full exercise duration.

Results

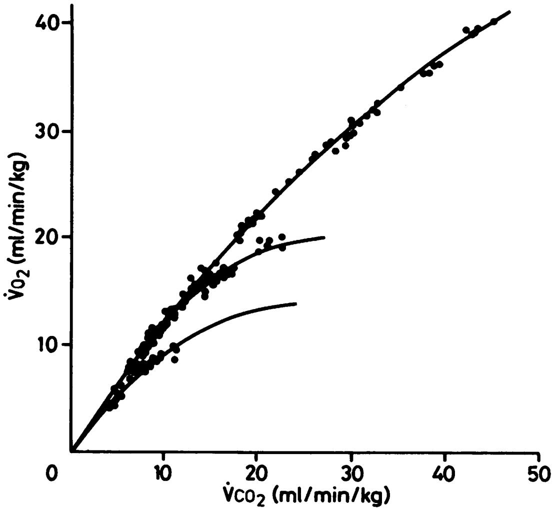

Fig 3 *Relation between the rate of oxygen consumption ($\dot{V}O_2$) and the rate of carbon dioxide production ($\dot{V}CO_2$) for a healthy subject (upper curve), a patient with mild chronic heart failure, and a patient with severe chronic heart failure (middle and lower curves respectively). The "best fit" curve has been superimposed on each set of data.*

All exercise tests were performed without complication. Figure 3 shows examples of $\dot{V}O_2/\dot{V}CO_2$ data with the fitted curves superimposed. Table 1 shows the individual results for the full exercise duration. $\dot{V}O_2$ max ranged from 9·6 to 49·4 ml/min/kg. Extrapolated maximal oxygen consumption ranged from 9·9 ml/min/kg to 52·2 ml/min/kg and correlated closely with $\dot{V}O_2$ max ($r = 0{\cdot}99$, $p < 0{\cdot}001$). The mean value of $\dot{V}O_2$ max expressed as a percentage of extrapolated maximal oxygen consumption was 95·6 (4·7%) with a range of 85·1% to 102·8%. The mean correlation coefficient for curve fitting was 0·91 (0·06) (range 0·73 to 0·98).

REPRODUCIBILITY OF EXTRAPOLATED MAXIMAL OXYGEN CONSUMPTION

Twelve subjects (three controls and nine patients) underwent a second exercise test in order to determine the reproducibility of extrapolated maximal oxygen consumption. When the second exercise test was compared with the first there was no relation between the error variance and extrapolated maximal oxygen consumption ($r = 0{\cdot}06$). Therefore the group was analysed as a whole. The retest reliability coefficient for extrapolated maximal oxygen consumption was 92·8%.

DEPENDENCE OF EXTRAPOLATED MAXIMAL OXYGEN CONSUMPTION AND $\dot{V}O_2$ ON EXERCISE DURATION

Table 2 gives the results for the three subsequent

Table 2 *Individual results for intermediate durations of exercise*

	90% exercise duration				*75% exercise duration*				*66% exercise duration*			
Subject	$\dot{V}O_2$	$\%\dot{V}O_2max$	*EMOC*	*%EMOC 100*	$\dot{V}O_2$	$\%\dot{V}O_2max$	*EMOC*	*%EMOC 100*	$\dot{V}O_2$	$\%\dot{V}O_2max$	*EMOC*	*%EMOC 100*
1	44·4	89·8	48·6	93·1	32·6	65·9	41·7	80·0	28·9	58·5	40·8	78·2
2	33·8	84·9	42·0	94·0	29·1	73·2	42·9	96·0	29·1	73·2	47·8	106·9
3	34·1	91·8	35·3	97·8	29·4	79·3	35·4	98·0	23·8	64·1	35·0	96·9
4	30·8	91·3	34·3	98·2	24·6	73·0	36·1	103·5	23·3	69·1		
5	30·7	91·2	35·2	95·7	23·0	68·4	32·1	87·2	21·0	62·5	30·8	83·6
6	26·1	97·6	26·6	98·3	22·5	84·1	25·7	94·9	20·1	75·2	26·0	96·0
7	23·5	94·9	24·4	98·5	22·7	92·0	24·2	97·7	20·7	83·9	23·9	96·5
8	20·5	88·6	22·2	97·2	18·2	78·9	22·6	98·6	16·4	71·1	22·2	97·1
9	21·1	93·7	23·7	97·9	19·7	87·1	22·8	94·0	16·7	74·2	21·2	87·5
10	19·8	92·9	23·2	98·3	16·9	79·3	22·8	96·7	16·9	79·3	25·1	106·4
11	20·2	94·7	20·7	98·9	19·0	89·3	20·5	98·0	17·5	82·0	20·5	98·0
12	18·2	91·0	19·2	96·7	16·7	83·5	19·0	95·5	16·5	82·7	19·0	95·4
13	18·3	95·6	20·9	104·9	16·0	83·8	21·4	107·5	15·1	78·8	22·6	113·6
14	17·3	94·0	18·3	96·9	15·9	86·8	18·2	96·2	15·1	82·4	18·9	100·3
15	16·5	99·8	18·0	104·2	14·8	89·6	20·2	116·5	13·9	84·0		
16	13·9	95·1	15·2	100·8	13·3	90·9	15·7	104·0	12·3	83·9		
17	13·6	93·1	17·0	98·6	12·7	86·7	16·4	95·4	11·4	77·9		
18	13·7	100·0	14·4	98·8	13·2	95·8	14·5	99·7	13·2	95·8		
19	13·2	99·0	14·1	101·7	12·3	91·8	14·8	106·2	11·4	84·8		
20	11·8	90·6	11·6	91·6	11·8	90·6	11·6	91·5	11·8	90·6	11·7	91·7
21	12·2	95·2	14·7	103·3	12·0	93·5			11·9	92·4		
22	11·9	93·5	13·3	100·2	11·6	91·6	15·0	112·8	10·4	82·0	15·5	116·7
23	11·9	93·9	15·1	103·2	11·4	90·6	16·7	114·7	11·4	90·1		
24	12·0	100·0	13·0	102·4	12·0	100·0	14·6	115·1	11·3	94·8		
25	9·4	96·5	9·5	96·1	9·3	95·6	9·4	94·9	9·3	95·6	9·3	93·7
26	8·8	91·7	10·5	104·8	8·8	91·2	10·5	104·3	8·5	88·0	10·1	100·0
Max	44·4	100·0	48·6	104·9	32·6	100·0	42·9	116·5	29·1	95·8	47·8	116·7
Min	8·8	84·9	9·5	91·6	8·8	65·9	9·4	80·0	8·5	58·5	9·3	78·2
Mean		93·9		98·9		85·9		100·0		80·6		97·6
SD		3·6		3·5		8·6		8·7		10·1		9·8

$\dot{V}o_2$, measured rate of oxygen consumption; $\%Vo_2max$, rate of oxygen consumption expressed as a percentage of the measured maximal rate of oxygen consumption; EMOC, extrapolated maximal oxygen consumption; %EMOC 100, extrapolated maximal oxygen consumption expressed as a percentage of the value obtained with data for full exercise duration.

analyses of data for intermediate exercise durations. For each reanalysis the resulting values for $\dot{V}o_2$ and extropolated maximal oxygen consumption are given in both absolute units (ml/min/kg standard temperature and pressure (dry)) and as a percentage of the respective values for full exercise duration. Extrapolated maximal oxygen consumption was only calculated if the correlation coefficient (r) for the fitted curve was $>0{\cdot}70$. These criteria excluded nine subjects (1 control and eight patients) from the 66% analysis and one patient from the 75% analysis. Figure 4 summarises the results. Over the range of exercise duration studied $\dot{V}o_2$ was linearly related to exercise duration. At 66% exercise duration the mean value of $\dot{V}o_2$ was approximately 80% of the value for $\dot{V}o_2$ max. In contrast, extrapolated maximal oxygen consumption was effectively independent of exercise duration over the same range.

Discussion

Maximal exercise tests are difficult to perform, even for normal subjects, and unpleasant for subjects and patients alike. The common limiting symptoms are

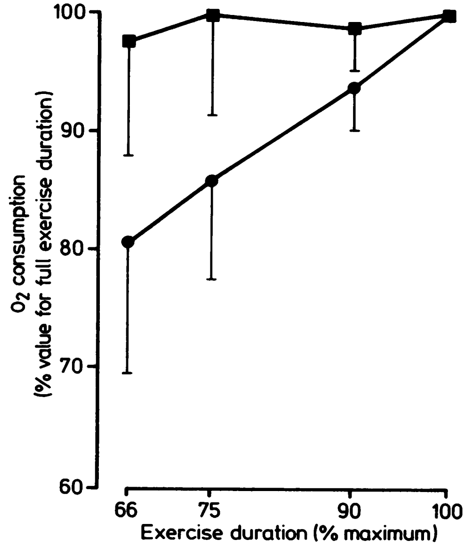

Fig 4 *Graphs showing the degree of dependence of measured oxygen consumption (●) and extrapolated maximal oxygen consumption (■) on exercise duration. Values are the mean for all 26 subjects. Bars represent one standard deviation.*

breathlessness and fatigue. The end point of a maximal exercise test (whether measured as duration, workload, or $\dot{V}O_2$ max) is unlikely to represent a standard end point for different individuals. Furthermore, the reproducibility of a symptom limited variable (desirable as it is for the assessment of response to treatment) adds no information about the cause or mechanism of limitation. For example, a stoic may repeatedly perform "truly" maximal exercise, whereas another individual with identical cardiorespiratory reserve may consistently stop at much lower levels of symptoms. It follows that if an absolute measure of cardiorespiratory functional capacity is required it should not depend purely on measure-ment of limitation caused by symptoms.

In this paper we present a new method for the analysis of respiratory gas exchange during exercise. This method provided an objective measurement of cardiorespiratory functional reserve that, within limits, was independent of exercise duration. We also showed that extrapolated maximal oxygen consumption correlated closely with $\dot{V}O_2$ max ($r = 0{\cdot}99$ $p < 0{\cdot}001$) in a study population selected for their ability to perform exercise that stressed cardiorespiratory function.

On average $\dot{V}O_2$ max was 4·4% lower than extrapolated maximal oxygen consumption and no subject achieved a value of $\dot{V}O_2$ max that was significantly greater than the value of extrapolated maximal oxygen consumption. These two findings add further support to the concept that extrapolated maximal oxygen consumptions provides a measurement of cardiorespiratory reserve.

Inherent in the calculation of extrapolated maximal oxygen consumption is the fact that respiratory exchange at extrapolated maximal oxygen consumption was double that at the onset of exercise (that is a/2). In non-mathematical terms, extrapolated maximal oxygen consumption may be envisaged as the value of $\dot{V}O_2$ obtained by extrapolating the relation between $\dot{V}O_2$ and $\dot{V}CO_2$ to the point at which respiratory exchange has risen to double the value at the start of exercise. Clearly it is essential that the curve accurately fits the raw data. The mean correlation coefficient of 0·91 obtained with the equation $y = ax - bx^2$ supports the use of this model. To obtain a value for extrapolated maximal oxygen consumption it is not necessary for the subject to exercise to these values of $\dot{V}O_2$ or respiratory exchange (which may be symptomatically intolerable if not physiologically impossible). It is only necessary to obtain sufficient data accurately to fit the curve.

We do not regard extrapolated maximal oxygen consumption as a replacement for $\dot{V}O_2$ max but rather as a complementary measurement that allows more information to be extracted from a single exercise test. If the values of $\dot{V}O_2$ max and extrapolated maximal oxygen consumption are similar this is evidence that the subject has performed close to "truly" maximal exercise. Alternatively, if the values are widely separated, it is likely that the subject either has a low threshold for symptoms or was limited by factors other than cardiorespiratory function. Because extrapolated maximal oxygen consumption is relatively independent of exercise duration it may avoid spurious variation in measured exercise capacity caused by differences in motivation or supervisor encouragement.

The equation $y = ax - bx^2$ provides an accurate mathematical model for the analysis of respiratory gas exchange during exercise. With this model it is possible to derive a measurement of cardiorespiratory functional reserve that is, within limits, independent of exercise duration. This measurement is complementary to $\dot{V}O_2$ max and greatly enhances the information obtained from a single exercise test.

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