

ORIGINAL ARTICLE

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Association between the anaerobic threshold and the break-point in the double product/work rate relationship

Abstract A break point in the double product versus work rate relationship (DPBP) during incremental exercise has previously been reported. The aim of the current study was to investigate the frequency and degree of inter-observer agreement with which a DPBP could be detected. We also wished to determine its relationship, if any, to the lactic acidosis threshold (LAT_{la}). Ten normal volunteers performed continuous incremental bicycle ergometer exercise under three different concentrations of inspired oxygen ($F_iO_2 = 0.21, 0.15$ and 0.12). In addition, a group of patients with diseases expected to result in impaired exercise tolerance performed exercise under room air conditions. Gas exchange was measured continuously and double product was measured at 15-s intervals throughout exercise using an automated sphygmomanometer. Four observers, unaware of subject identity and test condition, analysed a total of 39 tests. All four observers detected a DPBP in 29 cases (74%) and an LAT_{la} in 35 cases (90%). The intra-class correlation coefficient was 0.76 for the DPBP and 0.93 for the LAT_{la} , indicating a reasonable level of agreement among observers for both break points. The DPBP was

closely related to the LAT_{la} ($r = 0.865, P < 0.0001$), although it occurred at a slightly higher oxygen consumption ($\dot{V}O_2$, bias $0.137 \text{ l} \cdot \text{min}^{-1}$; 95% confidence intervals $0.041\text{--}0.233$). We conclude that the DPBP is a common occurrence during incremental exercise. The close relationship between the DPBP and the LAT_{la} suggests that both may reflect similar events at the level of the skeletal muscle cell.

Key words Double product/work rate break point · Incremental exercise · Anaerobic threshold · Lactic acidosis threshold

Introduction

Threshold phenomena in several variables are known to occur during incremental exercise. The most widely recognized is the anaerobic threshold, the point at which anaerobic production of high-energy phosphate compounds supplements aerobic production. The anaerobic threshold is accompanied by a net increase in lactate production. The gas exchange analogue of the anaerobic threshold, the lactic acidosis threshold (LAT_{la}), results from bicarbonate buffering of lactic acid and is marked by excess CO_2 production relative to O_2 consumption (Beaver et al. 1986). The LAT_{la} has found application in training regimens for athletes and in assessment of disease states (Matsumara et al. 1983; Smith and O'Donnell 1984; Packer 1987; Bogaard et al. 1988). In addition thresholds in ventilation (Whipp and Davis 1979), catecholamines (Mazzeo and Marshall 1989) and salivary electrolytes (Chicharro et al. 1994) have been described.

Heart rate and systolic blood pressure both rise throughout exercise. Recently the existence of a threshold in double product (the product of heart rate and systolic blood pressure) has been reported (Tanaka et al. 1995, 1996). The double product break point (DPBP) was measured in both young normal subjects and cardiac patients and appeared to be coincident with the LAT_{la} .

The aim of the current study was to determine if a DPBP could be measured in a group of normal volunteers exercising under different conditions known to alter the LAT_{la} and in a heterogeneous group of patients with impaired exercise capacity. In addition, we wished to

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investigate the level of agreement among several observers in detection of the break points and whether there was a systematic association between the LAT_{1a} and the DPBP.

Methods

Subjects

Normal volunteers

Ten healthy subjects, nine male and one female, were recruited. Their characteristics are shown in Table 1.

Patients

In order to increase the range of exercise tolerances under investigation, a group of ten patients was studied. This comprised six men with coronary artery calcification (in at least two major coronary arteries), two women with primary pulmonary hypertension, one man with myophosphorylase deficiency (McArdle's disease) and one man with phosphofructokinase deficiency. All were undergoing exercise testing as part of their clinical assessment. Their characteristics are shown in Table 1.

Ethical approval for the study was granted by the Harbor-UCLA Human Subjects Committee. Written informed consent was given by all subjects.

Experimental protocol

Subjects presented to the laboratory at least 2h after a light meal. After prior familiarization, a continuous incremental bicycle ergo-

meter exercise test was performed to each subject's symptom-limited maximum. Normal subjects visited the laboratory on three separate occasions to perform exercise while breathing one of three different inspired O_2 concentrations, namely air ($F_iO_2 = 0.21$), mild hypoxia ($F_iO_2 = 0.15$), and moderate hypoxia ($F_iO_2 = 0.12$). The hypoxic mixtures were obtained by mixing compressed N_2 with room air using a Venturi mixing valve, and were verified continuously during each test by a mass spectrometer (see later). The gases were humidified and breathed from a large breathing bag (140 l capacity) in all cases. The order in which the three tests were carried out was randomized and an interval of at least 2 days was allowed between tests. The subjects were not told the F_iO_2 of the gas in the bag. All tests consisted of a period of 10 min of rest, 3 min of unloaded pedalling, the incremental work period and finally a 3-min recovery period. The work rate increment was individually chosen for each subject (Table 1) according to their predetermined exercise tolerance so that the incremental period lasted between 8 and 15 min (Buchfuhrer et al. 1983). The work rate increment was the same in any individual for all tests. Breath-by-breath gas exchange measurements were carried out for the entire duration of the test and measurements of double product were performed at 15-s intervals from the beginning of unloaded pedalling to the end of the test. An electrically braked ergometer was used in all tests (Quinton Corival) and subjects maintained a pedalling frequency of 60–75 min^{-1} .

The patients were studied as already described, under normoxic conditions. They did not perform the hypoxia experiments. Since patients breathed only room air, the need for the breathing bag was obviated.

Gas exchange measurements

Subjects breathed through a mouthpiece attached to a volume turbine transducer (Alpha Technologies, Laguna Niguel, Calif., USA) for determination of inspired and expired volumes. Gas

Table 1 Subject characteristics and rate (slope) of increasing work rate

Subject	Disease	Sex	Age (years)	Height (m)	Mass (kg)	Work rate slope ($W \cdot min^{-1}$)	$\dot{V}O_{2max}$ ($l \cdot min^{-1}$)
Normals:							
1		m	24	1.80	87	25	3.10
2		m	29	1.57	70	25	3.15
3		m	42	1.75	82	15	2.28
4		f	24	1.78	56	15	2.08
5		m	55	1.78	69	20	2.35
6		m	34	1.85	85	30	4.10
7		m	30	1.88	87	30	3.43
8		m	30	1.57	75	30	3.55
9		m	42	1.73	74	20	2.57
10		m	41	1.52	49	20	2.43
Mean			35.1	1.72	73.4	23.0	2.90
(SD)			(9.8)	(0.12)	(13.0)	(5.9)	(0.66)
Patients:							
1	CAC	m	54	1.78	71	20	1.74
2	CAC	m	72	1.79	84	15	2.24
3	CAC	m	66	1.80	79	20	1.65
4	CAC	m	73	1.75	73	15	1.25
5	CAC	m	61	1.83	78	20	2.06
6	CAC	m	75	1.70	86	20	1.76
7	PPH	f	32	1.57	56	10	0.81
8	PPH	f	32	1.75	90	5	1.14
9	PFK	m	33	1.80	109	10	1.32
10	MPD	m	40	1.83	82	10	1.40
Mean			53.8	1.76	80.8	14.5	1.54
(SD)			(18.0)	(0.08)	(13.8)	(5.5)	(0.43)

[CAC Coronary artery calcification, PPH primary pulmonary hypertension, MPD myophosphorylase deficiency (McArdle's disease), PFK phosphofructokinase deficiency]

samples were drawn continuously from a side port of the mouth-piece for analysis of fractional concentrations of O₂, CO₂ and N₂ by a mass spectrometer (Perkin-Elmer, Oakbrook, Ill., USA). The analogue signals from the turbine and mass spectrometer were digitized at a resolution of 50 Hz. After time alignment of the turbine and mass spectrometer signals, to allow for mass spectrometer time delay, these digitized values were cross-multiplied and integrated for each individual breath to give breath-by-breath volumes of O₂ consumption and CO₂ production as previously described (Beaver et al. 1981). Breath-by-breath values were then converted to minute rates by taking breathing frequency into account. This resulted in on-line calculation of minute ventilation (\dot{V}_E), O₂ consumption ($\dot{V}O_2$) and CO₂ production ($\dot{V}CO_2$).

Double product measurements

Systolic blood pressure and heart rate were measured non-invasively using an automated sphygmomanometer (Kyokko-Busan, Tokyo, Japan). This machine has a three-lead electrocardiograph input and is capable of performing repeated determinations at 15-s intervals under computer control. The systolic blood pressure, heart rate and double product outputs from the sphygmomanometer were sent on-line to a PC for storage and subsequent analysis. Validation of the sphygmomanometer was performed for six subjects during exercise using simultaneous measurements of blood pressure at the other arm with a mercury sphygmomanometer.

Analysis of data

Breath-by-breath gas exchange measurements were interpolated, second-by-second, and time-averaged into 15-s periods. Plots of $\dot{V}CO_2$ versus $\dot{V}O_2$ were constructed and the LAT_{1a} was determined visually by four experienced observers working independently and following the method of Beaver et al. (1986). The computer files containing the blood pressure and double product data were merged with the corresponding files containing the work rate and gas exchange data. Plots of double product versus work rate were constructed and a break point in the relationship was sought visually, defined as the point at which a clear and sustained increase in the slope commenced. The $\dot{V}O_2$ at this work rate was determined from the $\dot{V}O_2$ versus work rate plot. All the plots were coded so that the observers did not know the identity of the subjects or the conditions of the test.

Statistical analysis

Differences among groups were assessed using ANOVA. Post-hoc pairwise comparisons were carried out using Scheffé's test. Agree-

ment between the two techniques was measured using the method of Bland and Altman (1986). The degree of reliability and agreement among the observers in determination of the LAT_{1a} and DPBP was assessed by calculating the intra-class correlation coefficient (Fleiss 1985).

Results

Validation of automated sphygmomanometer

The automated sphygmomanometer was found to give very similar readings of systolic blood pressure during exercise when compared with the manual method. The bias (manual-automated was 1.25 mmHg [95% Confidence intervals (CIs) -2.46 and 4.96; $n = 78$].

Main study results

All subjects completed the study uneventfully apart from subject number ten who became light-headed without hypotension during his moderate hypoxia test ($F_iO_2 = 0.12$). This particular test was aborted during the pre-exercise resting period. Overall therefore, a total of 39 tests were available for analysis. Peak exercise work rate, $\dot{V}O_{2max}$, respiratory exchange ratio (R) \dot{V}_E , heart rate, systolic blood pressure and double product are presented in Table 2. A gas exchange LAT_{1a} was able to be determined by all four observers in 35 tests overall (90%), and in 28 of the 30 tests (93%) in the normal subjects. Failure to find an LAT_{1a} occurred for the patient with myophosphorylase deficiency (two observers), the patient with phosphofructokinase deficiency (three observers), in the mild hypoxia test ($F_iO_2 = 0.15$) of normal subject number three (one observer) and the normoxia test ($F_iO_2 = 0.21$) of normal subject number seven (one observer). A DPBP was determined by all observers in a total of 29 cases (74%), including the patients with myophosphorylase and phosphofructokinase deficiency. Both break points were determined by all observers in 25 cases (64%). These data are summarized in Tables 3 and 4.

Table 2 Cardiovascular, ventilatory and gas exchange measurements at peak exercise during air ($F_iO_2 = 0.21$), 15% O₂ ($F_iO_2 = 0.15$) and 12% O₂ breathing ($F_iO_2 = 0.12$). ($\dot{V}O_2$ Maximal oxygen consumption, \dot{V}_E minute ventilation, R respiratory exchange ratio)

Parameter	Normal subjects		Patients	
	$F_iO_2 = 0.21$	$F_iO_2 = 0.15$	$F_iO_2 = 0.12$ ($n=9$)	$F_iO_2 = 0.21$
Peak work rate (\dot{W})	263 (63)	243 (54)*	221 (47)***	118 (56)****
$\dot{V}O_{2max}$ ($l \cdot min^{-1}$)	2.90 (0.66)	2.77 (0.58)	2.21 (0.44)****	1.54 (0.44)****
\dot{V}_E ($l \cdot min^{-1}$)	135 (28)	139 (28)	142 (21)	70 (14)****
R	1.22 (0.06)	1.24 (0.05)	1.34 (0.08)	1.18 (0.14)
Heart rate (beats $\cdot min^{-1}$)	177 (15)	171 (14)*	173 (14)*	148 (24)***
Systolic blood pressure (mmHg)	205 (40)	203 (33)	213 (29)	183 (36)
Double product/100 (mmHg beats $\cdot min^{-1}$)	363 (79)	346 (54)	367 (61)	270 (68)***

* $P < 0.05$ vs $F_iO_2 = 0.21$, ** $P < 0.05$ vs $F_iO_2 = 0.15$, ANOVA with Scheffé test. *** $P < 0.02$, **** $P < 0.0001$ vs normals ($F_iO_2 = 0.21$), unpaired t -test

Table 3 Numbers of cases in which a lactic acidosis threshold (LAT) and a break point in the double product versus work rate relationship (DPBP) could be detected by all four observers. The component of double product judged to be primarily responsible for the DPBP is also shown

Parameter	Normal subjects		Patients	
	$F_iO_2 = 0.21$	$F_iO_2 = 0.15$	$F_iO_2 = 0.12$	$F_iO_2 = 0.21$
Total number of cases (<i>n</i>)	10	10	9	10
LAT _{la} detected by all observers (<i>n</i>)	9	9	9	8
DPBP detected by all observers (<i>n</i>)	6	8	6	9
Heart rate primarily responsible for DPBP (<i>n</i>)	3	6	3	4
Systolic blood pressure primarily responsible for DPBP (<i>n</i>)	3	2	3	5

Of the 29 cases in which a DPBP could be determined by all observers, a break in the heart rate response was primarily responsible in 16 cases and a break in the systolic blood pressure in 13 cases (Table 3 and Fig. 1). However, breaks in both heart rate and blood pressure responses were contributory in 22 cases.

Inter-observer agreement and variability in identification of the LAT_{la} and DPBP were determined for those cases in which break points were identified by all observers (Table 4). The intra-class correlation coefficients for determination of the break points are also shown. Agreement was closer for the determination of the LAT_{la} than for the determination of the DPBP. ANOVA did show significant differences among observers for the LAT_{la} determination, but the intra-class correlation coefficient is a better guide to inter-observer agreement (Fleiss 1985). The inter-observer variability in determining the LAT_{la} and the DPBP is also shown in Fig. 2 for each individual subject and F_iO_2 condition.

The degree of association between the LAT_{la} and the DPBP is illustrated for each observer individually in Fig. 3. Those cases in which no break point was determined are plotted as 0, but are excluded from the correlation calculation. The overall correlation for the 25 cases in which both an LAT_{la} and DPBP could be determined by all observers was 0.865, $P < 0.0001$. Table 5 shows the mean values for each observer for the cases in which all observers found both break points. Figure 4 shows the pooled data in a Bland and Altman plot, where each point represents the mean of the values determined by the four observers. The bias (\bar{d} ; DPBP – LAT_{la}) was $0.137 \text{ l} \cdot \text{min}^{-1}$ (95% CIs 0.041 and 0.233).

In the normal volunteers, both the LAT_{la} and the DPBP were found to decrease with decreasing F_iO_2 (Fig. 5). ANOVA indicated no difference in the pattern of decrease ($P = \text{NS}$), although the mean DPBP was greater than the LAT_{la} ($P < 0.05$) for normal subjects and patients. The LAT_{la} expressed as a percentage of $\dot{V}O_{2\text{max}}$

Fig. 1 Contribution of heart rate and systolic blood pressure profiles to the double product break point (DPBP) A where a heart rate break point is the major contributor and B where a systolic blood pressure break point is the major contributor. Dotted lines indicate the mean DPBPs selected by the four observers

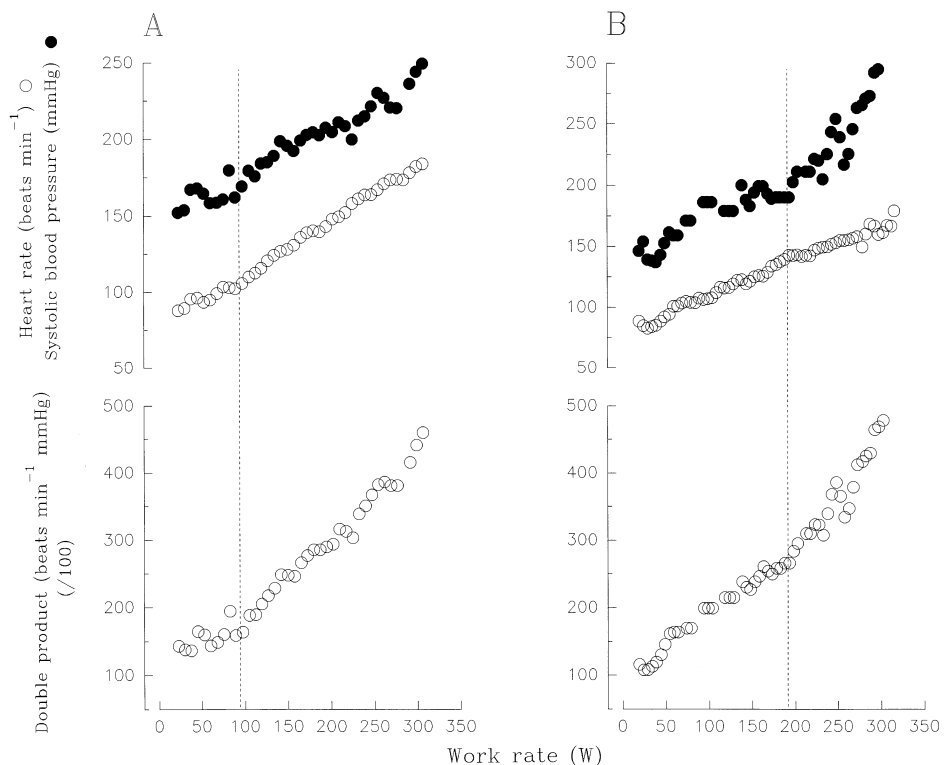


Table 4 Variability among observers in finding the LAT_{La} and DPBP

Observer	$\dot{V}O_2$ at LAT _{La} (l·min ⁻¹) (n = 35)	Work rate at DPBP (W) (n = 29)	$\dot{V}O_2$ at DPBP (l·min ⁻¹) (n = 29)
A	1.317 (0.390)	96.7 (51.1)	1.412 (0.610)
B	1.328 (0.376)	93.3 (37.7)	1.367 (0.436)
C	1.243 (0.358)*	92.2 (37.3)	1.364 (0.451)
D	1.223 (0.355)*	90.0 (34.0)	1.358 (0.418)
All	1.278 (0.369)	93.0 (40.1)	1.375 (0.479)
Intra-class correlation coefficient	0.93	0.76	

* $P < 0.05$ vs observers A and B, ANOVA with Scheffé test

was 49 (2)% ($F_iO_2 = 0.21$), 51 (3)% ($F_iO_2 = 0.15$), 52 (2)% ($F_iO_2 = 0.12$) in normal subjects and 63 (5)% ($P < 0.05$ versus other groups) in patients. The respective values for the DPBP were 57 (2)%, 55 (5)%, 59 (3)%, and 67 (3)% ($P < 0.05$, patients versus other groups).

Discussion

This study demonstrates that a break point often occurs in the double product/work rate relationship during incremental bicycle ergometer exercise. The break point is fairly robust, being present both in normal individuals exercising under three different F_iO_2 conditions and in a heterogeneous group of patients with impaired exercise tolerance. The double product is the product of heart rate and systolic blood pressure, and the break point appears to be determined by break points in either or both of these elements, but in different proportions in different tests. Since some cases had a break point in only one of the two components (e.g. Fig. 1), the measurement of the combined variable gives more information than does the measurement of either heart rate or systolic blood pressure alone.

There was reasonable agreement in determination of the DPBP among the four observers, as measured by the intra-class correlation coefficient. However, there was better agreement in the determination of the LAT_{La} than the DPBP (Table 4, Fig. 2). The proportion of tests in which an LAT_{La} was identified by all observers was also better than the proportion for the DPBP. Success in determination of the LAT_{La} was comparable with previous reports (Beaver et al. 1986; Shimizu et al. 1991; Elborn et al. 1994).

The V-slope method was used for the LAT_{La}. In this method the $\dot{V}O_2$ was selected at which $\dot{V}CO_2$ increased more rapidly than $\dot{V}O_2$ (slope greater than 1.0). The use of a 45° right-angled triangle aided this process since $\dot{V}O_2$ and $\dot{V}CO_2$ were plotted on x and y axes of equal length and scale. We chose to determine the LAT_{La} by inspection rather than by calculation. While the latter may result in the more precise localization of the LAT_{La}, the success in finding a break point is often not sig-

Table 5 Relationship between mean $\dot{V}O_2$ at LAT_{La} and DPBP for the 25 cases in which all observers determined a break point in both double product versus work rate and $\dot{V}CO_2$ versus $\dot{V}O_2$

Observer	LAT(l·min ⁻¹)	DPBP(l·min ⁻¹)	
A	1.297 (0.396)	1.430 (0.631)	$P = 0.05$
B	1.321 (0.388)	1.381 (0.448)	$P = NS$
C	1.221 (0.361)	1.388 (0.464)	$P < 0.05$
D	1.211 (0.363)	1.389 (0.422)	$P < 0.05$
All	1.263 (0.375)	1.397 (0.491)	$P < 0.01$

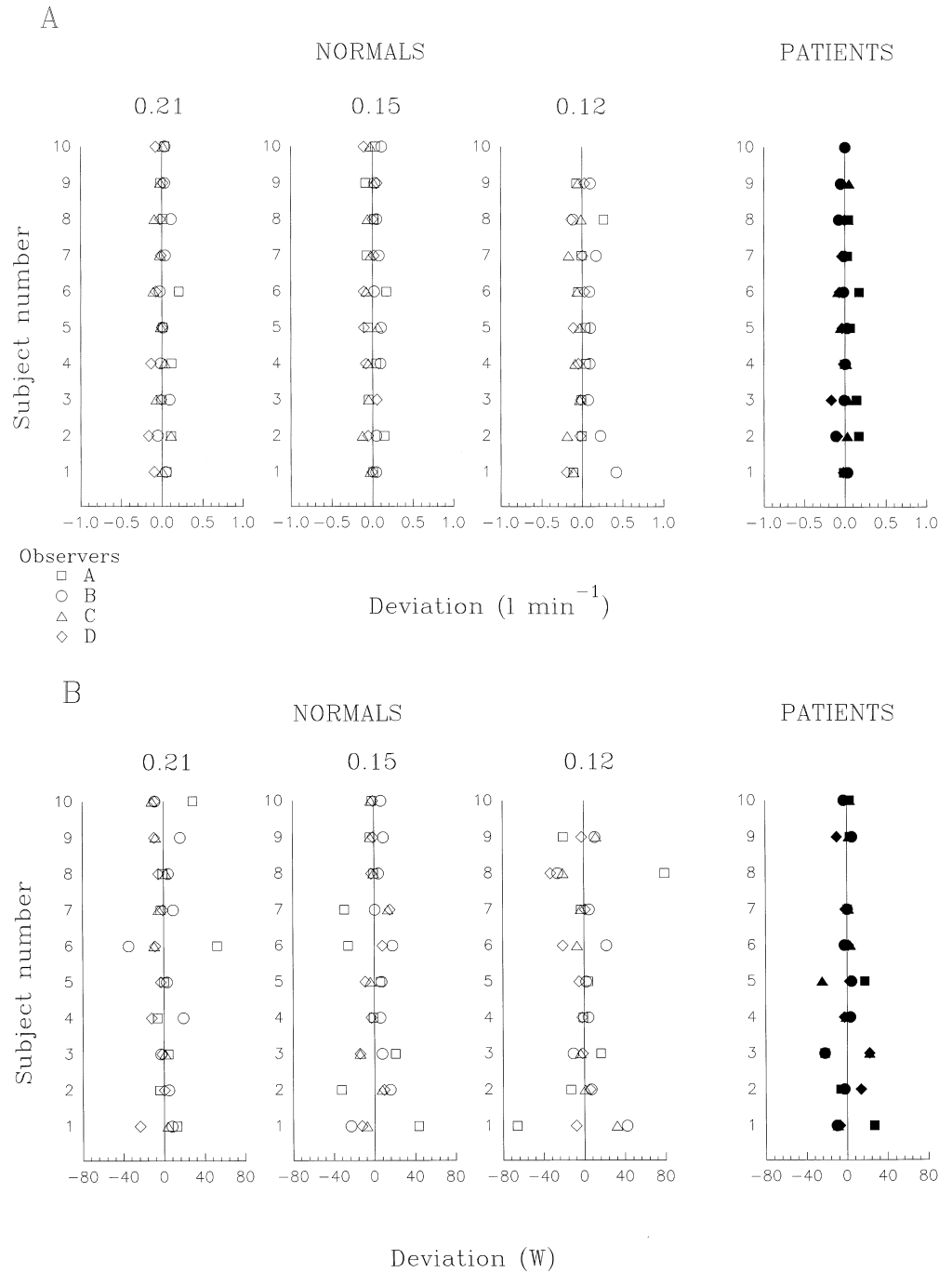
P values indicate significant differences between the $\dot{V}O_2$ at LAT_{La} and $\dot{V}O_2$ at DPBP; ANOVA with Scheffé test

nificantly greater than by inspection (Dickstein et al. 1990). Additionally, the computer programmes required are not widely available and even then are not easily adapted to analysis of the double product/work rate relationship.

Both the LAT_{La} and DPBP occurred at somewhat higher percentages of $\dot{V}O_{2max}$ in the patient group than in any of the studies in the normal subjects. The LAT_{La} tends to occur at quite high percentages of $\dot{V}O_{2max}$ in patients with cardiac disease (Elborn et al. 1994) and in other subjects with reduced $\dot{V}O_{2max}$ (Wasserman et al. 1987), but the reasons for this are unclear at present.

On average the DPBP occurred later than the LAT_{La} during incremental exercise. This is demonstrated by the small, but significant, bias in $\dot{V}O_2$ of approximately 0.1 l min⁻¹ (see Fig. 4). Nevertheless there was good correlation between the two measurements across the whole range of exercise performances studied, suggesting that there may be a link in their causation. It has previously been demonstrated that the LAT_{La} results from the evolution of CO₂ produced by bicarbonate buffering of lactic acid secondary to tissue anaerobiosis (Koike et al. 1990). The latter event is probably associated with cellular oxidative stress and a rise in circulating catecholamines. Noradrenaline and adrenaline levels in the blood have been shown to exhibit a threshold phenomenon which is closely related to the onset of blood lactate accumulation (Mazzeo and Marshall 1989; Chicharro et al. 1994; Weltman et al. 1994). Moreover, constant work rate endurance exercise

Fig. 2 Variability of determination of lactic acidosis threshold (LAT) (**A**) and double product break point (DPBP) (**B**) among the four observers in relation to experimental condition and group. Each determination is plotted as the deviation from the mean of all the determinations for each case. Please note that a break point was not determined by all observers in all cases. Normal subjects are shown as *open symbols* and patients as *closed symbols*. Each observer is shown as a *different shaped symbol*. Please see panel A for key



performed above the anaerobic threshold results in a disproportionate increase in noradrenaline and adrenaline compared with exercise performed at or below the anaerobic threshold (Urhausen et al. 1994). Since catecholamines induce rises in both heart rate and systolic blood pressure, it is possible that the DPBP is a consequence of a disproportionate rise in sympathetic activity. This may serve to improve blood flow and O_2 delivery to the working muscle. In the current study, the finding of a lower DPBP under conditions of simulated altitude is consistent with this hypothesis. Hypoxia would be expected to result in impairment of aerobic

ATP production by the muscle cell (Idstrom et al. 1985; Wolfe et al. 1988) and an early rise in sympathetic activity (Seals et al. 1991; Warner and Mitchell 1991). Lactate acting at the level of the peripheral circulation may stimulate cardiovascular responses directly and may be an additional factor in the close relationship between the DPBP and the LAT_{1a} (Thimm et al. 1984; Gregory et al. 1987). This latter possibility would be consistent with our finding that the DPBP occurs slightly later than the Th_{1a} .

Myophosphorylase deficiency and phosphofructokinase deficiency are both caused by abnormalities of

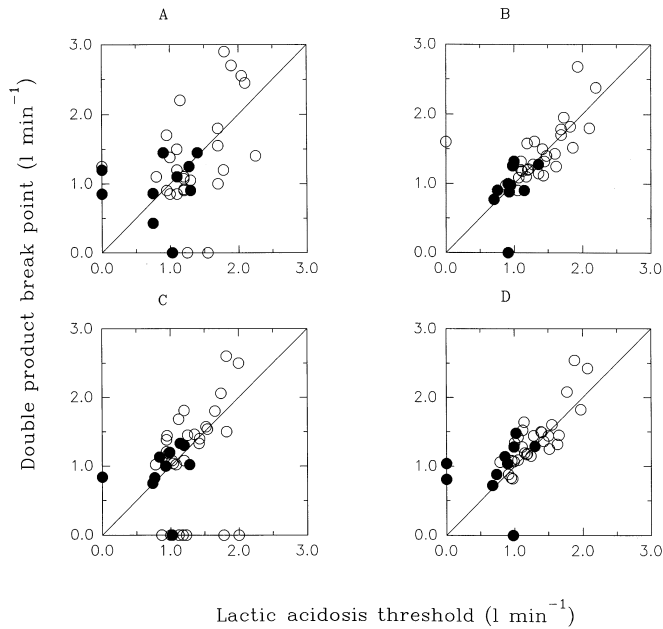


Fig. 3A-D Association between the LAT_{la} and the DPBP for each of the four observers. Normal subjects are illustrated by *open circles* and patients by *closed circles*. Those cases in which a break point was not identified are plotted as zero, but are excluded from the correlation analysis. The line in each case is the line of identity. Observer A: $r = 0.628$, $P < 0.0001$, $n = 33$; observer B: $r = 0.837$, $P < 0.0001$, $n = 37$; observer C: $r = 0.811$, $P = 0.0001$, $n = 30$; observer D: $r = 0.829$, $P < 0.0001$, $n = 36$

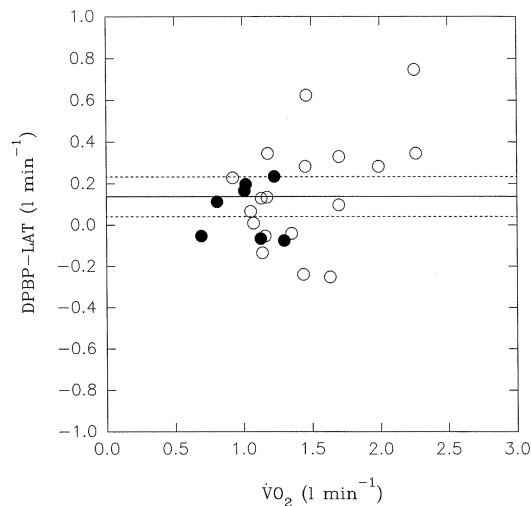


Fig. 4 Individual differences between the DPBP and LAT plotted as a function of their mean value. Normal subjects are illustrated by *open circles* and patients by *closed circles*. Each value is derived from the average value returned by all four observers. Only cases in which both break points were determined by all four observers are included ($n = 25$). The *solid line* indicates the bias (d) between the two measurements. The 95% confidence intervals are illustrated by the *broken lines*. The bias (d ; $DPBP - LAT$) was $0.134 \text{ l} \cdot \text{min}^{-1}$ (95% CIs $0.041-0.233$) and the correlation coefficient (r) was 0.865 ($P < 0.0001$)

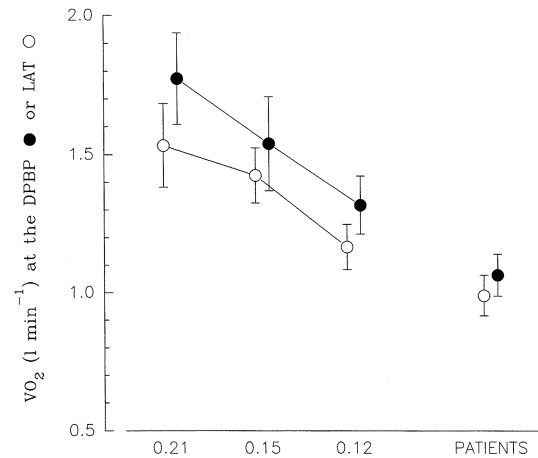


Fig. 5 Relationship between mean $\dot{V}O_2$ values at the LAT_{la} and DPBP illustrated for the patients and for the three different fractional concentration of O_2 in inspired gas (F_iO_2) experiments performed by the normal subjects. Only cases in which both break points were determined by all four observers are included ($n = 25$)

enzymes in the glycolytic pathway and result in impaired exercise tolerance and failure of lactate production by skeletal muscle. It is interesting that a clear DPBP was found by all observers in both patients with these diseases, whereas the LAT_{la} , as expected (Riley et al. 1993), was difficult to determine. This suggests that there may be a metabolic rate at which sympathetic activity rises abruptly and this rise may indicate a failure to maintain cellular energy supply in the working muscle. Failure to maintain cellular energy supply in myophosphorylase deficiency is signalled by rises in circulating ammonia and hypoxanthine (Brooke et al. 1983), and it would be interesting to know whether the DPBP is associated with rises in these substances.

In conclusion, we have confirmed the common, but not invariable, occurrence of a break point in the double product/work rate relationship during incremental exercise. This break point can be detected in a majority of exercise tests with a good level of inter-observer agreement and appears to be systematically related to the LAT_{la} . While this association suggests that both may be the result of linked phenomena, perhaps at the level of the exercising muscle, the mechanisms underlying the double product breakpoint merit further investigation.

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