



Correlation of the break point of the double product and the ventilatory thresholds

Correlación del punto de quiebre del doble producto y los umbrales ventilatorios

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Palabras clave:

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ABSTRACT

Introduction: during physical exercise with incremental load, the double product is increased by sympathetic stimulus, and its increase presents a positive inflection called the double product breaking point or break point of double product (BPDP). Commonly, there is a correlation between this and the lactic threshold (LT), but we do not know its association with the ventilatory thresholds that are usually used to prescribe training. **Objective:** to determine the correlation of the BPDP with the ventilatory thresholds. **Material and methods:** a descriptive, prospective, analytical, non-randomized study was carried out in which patients with heart disease who underwent maximal cardiopulmonary exercise tests were included. The PD was obtained and plotted as a function of time (every minute) to establish the BPDP by line drawing. The correlation was made with the ventilatory thresholds obtained from the CPET gas analysis using the ventilatory equivalents method. **Results:** twenty-one patients between 49 and 59 years old (14.3% women) were studied. The Spearman correlation coefficient was applied, and it was found that there is a strong-moderate positive correlation between BPDP and VAT-DP with statistical significance ($p = 0.004$, $r = 0.60$) and in the same way between BPDP and moderate correlation with VT2-DP ($p = 0.005$, $r = 0.59$). **Conclusion:** determination of PD is a reproducible and easily accessible method for determining ventilatory thresholds. The BPDP correlates with the aerobic-anaerobic ventilatory threshold (VAT), determining training intensity in patients with heart disease.

RESUMEN

Introducción: durante el ejercicio físico en carga incremental se eleva el doble producto por estímulo simpático y su incremento presenta una inflexión positiva denominada punto de quiebre del doble producto (PQDP). Comúnmente existe una correlación entre éste y el umbral láctico (UL), pero desconocemos su asociación con los umbrales ventilatorios que suelen emplearse para la prescripción del entrenamiento. **Objetivo:** determinar la correlación del PQDP con los umbrales ventilatorios. **Material y métodos:** estudio descriptivo, prospectivo, analítico, no aleatorizado, se incluyeron pacientes con cardiopatía que realizaron prueba máxima de ejercicio cardiopulmonar. Se obtuvo el DP y se graficó en función del tiempo (cada minuto) para establecer mediante trazado de rectas el PQDP. Se hizo la correlación con los umbrales ventilatorios obtenidos del análisis de gases del CPET, por método de los equivalentes ventilatorios. **Resultados:** se estudiaron 21 pacientes entre 49 y 59 años (14.3% mujeres). Se aplicó el coeficiente de correlación de Spearman y se encontró que existe una fuerte-moderada correlación positiva entre el PQDP y el VAT-DP con significancia estadística ($p = 0.004$, $r = 0.60$) y de la misma manera entre PQDP y correlación moderada con VT2-DP ($p = 0.005$, $r = 0.59$). **Conclusión:** la determinación del DP es un método reproducible y de fácil acceso para determinación de umbrales ventilatorios. El PQDP correlaciona con el umbral ventilatorio aeróbico-anaeróbico (VAT), por lo que puede ser utilizado para determinar la intensidad en el entrenamiento de los pacientes con cardiopatías.

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Abbreviations:

BMI = Body mass index.
 BDP = Break point of double product.
 CO = Cardiac output.
 CPET = Cardiopulmonary exercise test.
 DP = Double product.
 HR = Heart rate.
 LT = Lactic threshold.
 MHR = Maximum heart rate.
 MVO₂ = Myocardial oxygen consumption.
 NYHA = New York Heart Association.
 PaCO₂ = Partial pressure of carbon dioxide.
 PETO₂ = End-tidal oxygen tension.
 RER = Respiratory Exchange Ratio.
 SBP = Systolic blood pressure.
 SPSS = Social Package for Social Sciences.
 VAT = Aerobic-anaerobic threshold.
 VCO₂ = CO₂ production.
 VE = Pulmonary ventilation.
 VO₂ = Oxygen consumption.
 VT = Ventilatory threshold.
 VT1 = 1st ventilatory threshold.

INTRODUCTION

Physical exercise is a stimulus that generates a body response, both centrally and peripherally, secondary to the increase in oxygen demand. The adaptations are immediate at the time of the effort and become chronic by maintaining the stimulus in a sustained manner. With the start of exercise and its intensity increasing, the demand for oxygen increases, mainly due to the stimuli found in activity.¹ The magnitude of the hemodynamic response to exercise depends on the intensity, the muscle mass involved, and the ability of the heart to increase its stroke volume.¹

Blood pressure reflects cardiac output (CO), heart rate (HR), peripheral vascular resistance, and blood volume variations. Since 1972, Kimura et al. were the first to discuss the product of heart rate – blood pressure, or double product (DP), as a predictor of coronary blood flow and myocardial oxygen consumption (MVO₂) in healthy young subjects.^{1,2} DP is the index that best correlates with MVO₂ in patients with ischemic heart disease.³ Plasma catecholamine concentration rises exponentially with increasing workloads;⁴ this event is influenced by the increased stimulation of the sympathetic nervous system

that occurs above the lactate threshold and a gradual decrease in parasympathetic activity. Likewise, there is a disproportionate increase in systolic blood pressure above the ventilatory threshold.⁵ During the incremental load exercise, the slope of the double product presented a positive inflection called the break point of double product (BDP),⁶ and the same phenomenon occurs in a similar way to the lactic threshold (LT), keeping a strong relationship with the ventilatory threshold (VT) described by Wasserman.^{7,8} The anaerobic threshold or VT can be identified using several markers that represent different physiological systems,^{4,7,9-13} including the double product.¹⁴⁻²⁰

Tanaka et al. found that the DP increases steeply above the LT, and, as a result, the BDP is considered a valid and useful parameter as a marker of the LT.^{6,14} According to the Skinner and McLellan triphasic model, incremental load exercise is structured in three phases or stages of increasing intensity from rest to maximum intensity.²⁰ These phases are:

1. Phase I. An increase in CO₂ production (VCO₂) occurs in relation to oxygen consumption (VO₂) and cellular lactate buffering.
2. Phase II. By increasing VCO₂, there is a proportional increase in pulmonary ventilation (VE), keeping PaCO₂ constant, which is called «isocapnic buffering».
3. Phase III. Respiratory compensation of metabolic acidosis, with decreased PaCO₂.

Previously, the correlation of the break point of the double product as an indicator of the anaerobic threshold (LT or VT) has been pointed out, being consistent in patients with heart disease as well as in healthy subjects or athletes;^{21,22} however, there is little evidence of its correlation with ventilatory thresholds (VT1 and VT2). Due to its correlation with the LT and the more abrupt change in cellular metabolism during the incremental load of the oxidative system to the glycolytic system, the BDP could be more related to the ventilatory threshold (VT1). The objective of this work is to correlate BDP and ventilatory behavior during incremental load exercise in patients with heart disease.

Table 1: Demographic, comorbidity clinical, pharmacological, and biochemical characteristics of the study population. (N = 21).

Characteristics	n (%)
Demographics	
Age [years]	58 (49.5-59)
Gender	
Male	18 (85.7)
Female	3 (14.3)
Etiology	
Ischaemic cardiomyopathy	16 (76.2)
Chronic heart failure	5 (23.8)
Cardiac valve disease	2 (9.5)
Pulmonary arterial hypertension	1 (4.8)
Congenital heart disease	1 (4.8)
Comorbidities	
Dyslipidemia	8 (38.1)
Obesity	14 (66.7)
Type 2 diabetes mellitus	6 (28.6)
Systemic arterial hypertension	12 (57.1)
Smoking	8 (38.1)
Clinical	
BMI [kg/m ²]	28.6 (26.4-29.7)
LVEF [%]	55 (38-62)
Functional class	
1	17 (81.0)
2	3 (14.3)
3	1 (4.8)
IscT	4 (19.0)
ArrT	1 (4.8)
Pharmacological	
ACEI	10 (47.6)
ARA	4 (19.0)
AAP	18 (85.7)
Estatinas	18 (85.7)
BB	14 (66.7)
CA	4 (19.0)
Diuréticos	5 (23.8)
Biochemical, (mg/dL)*	
Glucose	99 [61.5-135.2]
C-HDL	29.3 [21.7-36.2]
C-LDL	72 [30.7-121.7]
Triglycerides	156 [50.2-233]

AAP = antiplatelet agents. ACEI = angiotensin converting enzyme inhibitor. ARA = angiotensin receptor antagonist. ArrT = arrhythmical threshold. BB = beta-blockers. BMI = body mass index. CA = calcium antagonists. IscT = ischaemic threshold. LVEF = left ventricular ejection fraction.

* Data are presented in means [p25-p75]

MATERIAL AND METHODS

This is a descriptive, prospective, analytical, non-randomized study at a cardiac rehabilitation center in Mexico City during the months of July to December 2020. The patients underwent a cardiopulmonary stress test under the ramped modified Bruce protocol on the treadmill. The inclusion criteria were patients with any heart disease older than 18 years and who had undergone cardiopulmonary testing (CPET, with expired gas analysis, BTL CardioPoint®-Ergo v. 2.33.201.0.a. Patients who had a contraindication to perform the test and had reason to suspend the study, also eliminating patients who did not perform a maximum exercise test or presented a hypotensive response associated with physical exercise. The criteria that determined the maximum were MHR > 85%, RER > 1.15, and Borg > 17). All participants signed informed consent regarding the risks and complications of performing the test. Ethics, research, and biosafety regulations were complied with.

For all the selected patients, a record of HR (automated) and blood pressure (manually with a sphygmomanometer by the doctor) was obtained every minute. The perception of effort was evaluated with the Borg scale.^{6-19,23} The DP was obtained using the formula $HR \times SBP$. The DP curve was plotted as a function of time, and by drawing straight lines on the figure, the point where an abrupt inflection occurred was sought to determine the BPDP. The analysis of the slopes plotted on the graph obtained was reviewed by experts in the area.

The ventilatory thresholds were obtained from the gas analysis of the CPET during the stress test, in curves 4 and 7 of Wasserman in the following way:^{7,11,20}

1. VT1: $\uparrow VE/VO_2 + \uparrow PETO_2$;
2. VT2: $\uparrow VE/VCO_2 + \downarrow PETCO_2$;
3. VAT: $RER (VCO_2/VO_2) = 1.0$.

Where VT1 is the 1st ventilatory threshold, defined as the turning point of the curve for the ventilatory equivalent of oxygen (VE/VO_2), and the positive inflection of the oxygen pressure at the end of expiration; VT2 is the 2nd ventilatory threshold, defined as the

break point of the curve for the ventilatory equivalent of carbon dioxide (VE/VCO_2), and the negative inflection of the carbon dioxide pressure at the end of expiration; and VAT is the aerobic-anaerobic threshold that is equivalent to the RER or respiratory quotient equal to 1.0 (crossing point of the VO_2 curve and elimination of carbon dioxide).¹¹ When there was doubt or discrepancy in the measurement of ventilatory thresholds through the method of equivalents that was used for this study, we resorted to the support of the V-slope. Subsequently, an analysis and correlation of the thresholds with respect to the BPDP was carried out.

Statistic analysis

The data was captured in a database in the Microsoft Excel program and analyzed in the statistical package Social Package for Social

Sciences (SPSS) version 24. For the continuous variables, the results were presented in medians and percentiles and as frequencies and percentages in the case of categorical variables. For the correlation of the variables of interest, the Spearman correlation coefficient was used. In all cases, moderate correlation coefficients > 0.50 and statistically significant values < 0.05 were taken.

RESULTS

A total of 21 patients with a mean age of 58 years (range 49.5 to 59 years) were included, where 85.7% were men and 14.3% were women. The average BMI was 27.6. The cardiovascular risk factors present were obesity, systemic arterial hypertension, smoking, dyslipidemia, and diabetes mellitus. The heart diseases presented by the patients are ischemic heart disease, heart failure, valve disease, one case of congenital heart disease, and one of pulmonary arterial hypertension. 81.8% were in NYHA functional class I and 13.6% in NYHA functional class II. *Table 1* shows the demographic data, comorbidities, pharmacological treatment, and biochemical characteristics of the study population.

All patients underwent cardiopulmonary testing. The most common reason for suspension was fatigue. Only four presented an ischemic threshold without limiting angina; none presented hypotensive response or important ventricular arrhythmias. There were no incidents or complications in all the exercise tests performed. It was possible to identify the BPDP and the ventilatory thresholds of all the chosen subjects. *Table 2* shows the results of the population characteristics of the stress test. An example of the determination of the double product breakpoint by plotting the double product against time during cardiopulmonary stress testing is shown in *Figure 1*.

The relationship between ventilatory thresholds (expressed in DP) and BPDP was analyzed. For this, the Spearman rank correlation coefficient was applied as a statistical method, and it was found that there is a strong-moderate positive correlation between the BPDP and the VAT-DP with statistical significance ($p = 0.004$, with values

Table 2: Characteristics of the stress test of the study population. (N = 21).

Characteristics	
HR (bpm)	68 (62-77.2)
M-HR (bpm)	152 (133-163.7)
SBP (mm/Hg)	120 (107.5-127.0)
M-SBP (mm/Hg)	155 (143.7-165.0)
METS	
M-METS	10.4 (8.3-12.3)
VO_2 (mL/kg/min)	
M- VO_2 (mL/kg/min)	2,591 (1,791.5-3,630.5)
B-DP*	8,430 [6,757.2-9,957.5]
VT1-DP*	11,410 [10,297.5-13,485]
VAT-DP*	18,300 [15,190-19,620]
VT2-DP*	20,580 [17,662.5-22,237.5]
M-DP*	23,210 [20,175-26,740]
BPDP*	16,090 [14,815-19,157.5]
VT1-T*	2.4 [2-4.1]
VAT-T*	8.7 [6.4-10.5]
VT2-T*	10.5 [9.1-12.7]
B = basal. BPDP = break point of the double product. DP = double product. HR = heart rate. M = maximum. METS = metabolic equivalent. SBP = systolic blood pressure. T = time. VAT = anaerobic aerobic ventilatory threshold. VO_2 = oxygen consumption. VT1 = ventilatory threshold 1. VT2 = ventilatory threshold 2. * Data are presented in medians [p25-p75].	

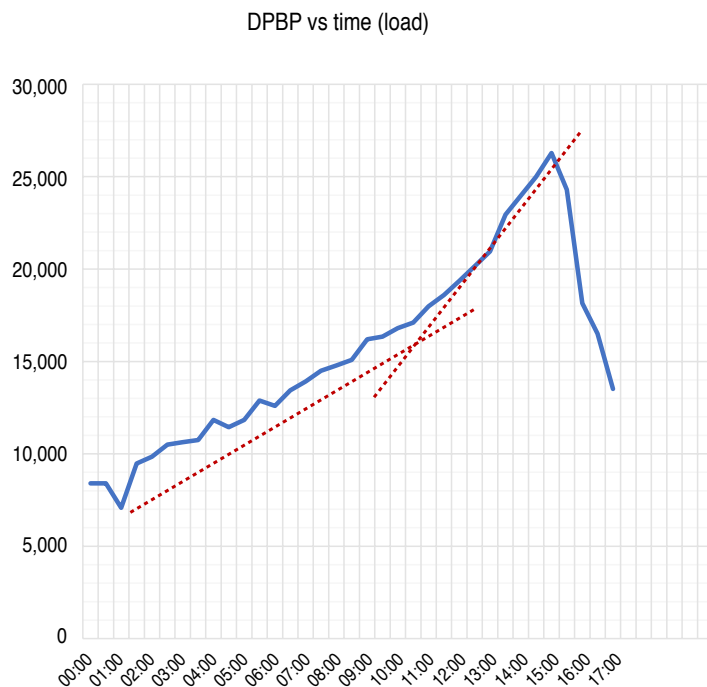


Figure 1: Calculation to determine the break point of the double product.
DPBP = double product break point.

of $r = 0.60$). The statistical method was also applied to the relationship between the BPDP and the VT2-DP, and it was observed that there was a positive and statistically significant correlation ($p = 0.005$, $r = 0.59$). Figure 2 shows these correlations using the Spearman method.

DISCUSSION

In the traditional determination of the change from aerobic or oxidative to anaerobic or glycolytic metabolism, the LT and VT were used in physiological terms as clear turning points in which a differentiation of the energy reserve used by the patient in an exercise in incremental load. For prescription purposes, this has always generated support for calculating the optimal level of intensity of aerobic endurance training in patients with heart disease. However, starting from the understanding that there is not only a clear point of inflection in which the metabolism changes from one energy reserve to another but also that it is an aerobic-anaerobic

transition zone determined by two ventilatory thresholds,^{11,20,24} BPDP analysis becomes a more imminent need for cardiac rehabilitators who want to specify their prescription in the absence of expired gas analysis.

Brubaker compared BPDP with VT (determined through V-Slope) in 88 patients with heart disease during incremental load exercise testing, finding a difference of 5% in VO_2 measured between thresholds (Pearson $r = 0.81$, $p < 0.001$) (fifteen). For his part, Riley compared a group of 10 healthy subjects and 10 with heart disease and found that the mean value in VO_2 of the BPDP was significantly higher than that of the LT in patients with heart disease, and the BPDP was correlated with the LT ($r = 0.865$, $p < 0.0001$), and LT is commonly associated with VT1.¹⁶ This contrasting evidence was what motivated the present investigation to find a more precise association with the BPDP. Although the V-Slope method is plausible for calculating VT, our study used the ventilatory equivalents methodology to find the most precise degree of correlation in the aerobic-anaerobic transition phase through the two thresholds, VT1 and VT2, with the intention of translating this correlation with the training prescription using the Skinner-McLellan triphasic scheme.

In addition to finding a correlation between the increase in DP before and after its breakpoint (286.2 vs 98.5/W, $p < 0.001$), Omiya found that BPDP had a strong correlation with VT ($r = 0.93$, $p < 0.01$) and LT ($r = 0.95$, $p < 0.01$), concluding that the BPDP can be used as an index of exercise intensity in patients with CAD similar to VT or LT. Another finding was that the non-invasive measurement of the BPDP is comparable to the invasive method.¹⁷

Hargens observed that, like the VT, the BPDP, after eight weeks of dynamic training, occurs at a higher intensity. He concluded that BPDP could be a useful marker for VAT ($\text{RER} = 1$), easier to obtain than VT or LT, using it in healthy populations as an independent parameter of exercise intensity.¹⁸ In our study, it was found that the threshold that most correlate with the BPDP is the aerobic-anaerobic ventilatory threshold (VAT);

although 4% of the patients studied matched it with VT1, it was not the objective of the study to correlate the displacement of the BPDP with some other threshold after the training process.

In our methodology, blood pressure measurement was determined manually (non-invasively), recording minute by minute, achieving an adequate graphical representation when determining the BPDP, consistently regardless of the magnitude of the increase in SBP or HR.^{22,23} The variation between the pressure increments was very stable, being carried out at intervals every 3 minutes without affecting the determination of the BPDP. Compared to previous studies,^{15,17,18,21,25} where automated and other invasive recordings are used, performing the measurement manually allows the double product to be reliably established, as well as its breakpoint.^{23,24} Although the degree of correlation measured by Spearman was not greater than 0.90 and therefore cannot be considered a surrogate methodology, the clinician's approach based on this BPDP measurement methodology may represent a more useful tool that could help determine the training intensity that ideally occurs between the ventilatory threshold phase.²⁶

More studies, with a larger volume of patients, are required to confirm these data and to elucidate in future research whether this BPDP manages to move towards VT2, as it usually happens physiologically when patients with heart disease adapt to a cardiac rehabilitation program based on physical training. One limitation of our study was not having correlated these thresholds with the lactate analysis, but their use is not routine or practical in the clinical evaluation of patients admitted to these programs. Therefore, the strength of our study lay in measuring, through the gold standard (the stress test with expired gas analysis), the training zones through the ventilatory thresholds.

CONCLUSIONS

The determination of DP is a reproducible and easily accessible method for determining ventilatory thresholds. The BPDP moderately correlates with the aerobic-anaerobic ventilatory threshold (VAT), so it can be used to determine the training intensity of patients with heart disease in the absence of cardiopulmonary exercise testing or lactate testing by defining the limit of the depletion of the oxidative reserve and, therefore, the beginning of metabolic instability.

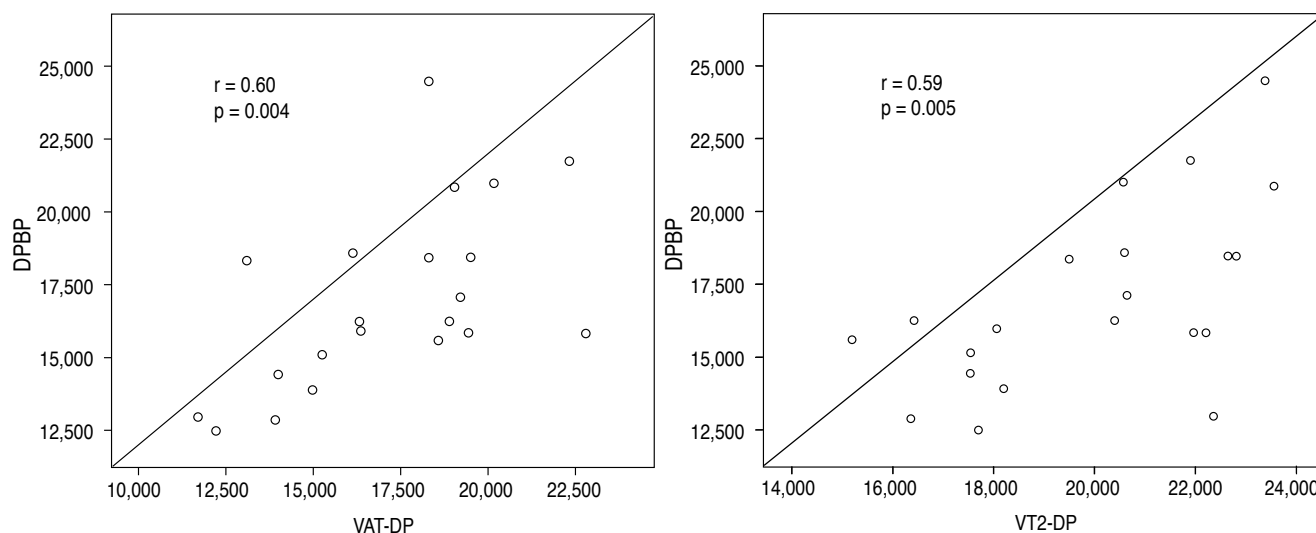


Figure 2: Spearman correlation between aerobic-anaerobic ventilatory threshold-double product (VAT-DP) and ventilatory threshold 2-double product (VAT-2-DP) with the calculated double product break point.

DPBP = double product break point.

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Declaration of confidentiality and patients

consent: the authors declare they have followed their workplace protocols for using patient data. Also, they certify that the patient has received sufficient information and has given written informed consent for his/her/their images and other clinical information to be reported in the journal, without names or initials, to protect the right to privacy.

Clinical trial registration and approval

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