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Original Article

Double product break point estimates ventilatory threshold in individuals with type 2 diabetes

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Abstract. [Purpose] To verify the identification of the anaerobic threshold through the double product breakpoint (DPBP) method for individuals with type 2 diabetes. [Subjects and Methods] Nine individuals with T2D (7 females; age=63.2 ± 8.9 y) and 10 non-diabetic (ND) (7 females; age=58.3 ± 7.8 y) performed an incremental exercise test on a cycle ergometer. Heart rate (HR), blood pressure (BP) and expired gas were measured at the end of each stage. The ventilatory threshold (VT) and DPBP were considered as the exercise intensities above which an over proportional increases in VE and DP were observed in relation to increasing workload. [Results] No differences were observed between the workloads, HR and VO_2 corresponding to the AT identified respectively by VT and DPBP. For the T2D, strong correlations between VT and DBPB workloads (r=0.853), HR (r=0.714), and VO_2 (r=0.863) were found. These relationships were similar to those found for the control group (r=0.923; r=0.881; and r=0.863, respectively). [Conclusion] These results demonstrate that the DPBP enables for the prediction of AT and correlated well the VT in both the T2D and ND participants.

Key words: Anaerobic threshold, Systolic pressure, Heart rate

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INTRODUCTION

The anaerobic threshold (AT) is a hallmark of the aerobic fitness of athletes[1)], physically active individuals[3)] and on a minor scale for special populations, such as individuals with type 2 diabetes (T2D)[2, 4, 5)]. AT has been considered the gold standard along with maximum oxygen consumption (VO_2max) for the evaluation of aerobic fitness and the subsequent prescription of aerobic exercise[6–9)]. Moreover, monitoring of aerobic training adaptations through AT determination may be especially interesting because no maximal effort is needed, and could be safer for individuals with pathologies such as hypertension and diabetes[10, 11)].

The AT can be identified using several markers representing different physiological systems. For instance, the AT has been determined through the analysis of heart rate variability (HRV)[2)], blood catecholamines[12)], blood glucose and lactate[3)], ventilation and respiratory equivalents[13, 14)], and the double product (DP)[15–22)].

Identification of AT through different indices, such as the double product (DP), has been widely utilized for healthy individuals[16, 17, 19)], athletes[20)] and individuals with cardiovascular diseases[15, 16, 18)]. However, few studies have identified the AT of individuals with T2D through different methods[2, 23)], while the exercise recommendations for T2D[24)] indicate that these patients should be encouraged to undertake an exercise test before being submitted to physical training. For instance, the AT

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of T2D individuals is often observed to be between 60–70% of VO_2max[6, 8, 25], which is an exercise intensity that has been widely recommended for this population for better blood glucose and cardiovascular control[24].

Further, previous studies have shown that aerobic exercises performed around AT intensities significantly reduced the blood pressure (BP) of individuals with T2D in the post-exercise period[6–8, 25, 26], and none of these previous studies reported complications during the experimental sessions, suggesting the desirability of AT identification for this population, since inadequate physical exertion can be a powerful triggering factor of myocardial infarction[27].

Individuals with T2D often present autonomic dysfunction[28–30]. Compared to healthy individuals, it is therefore likely that they would show a different hemodynamic reaction [heart rate (HR) and BP, and in turn DP] during exercise, such as an exaggerated exercise blood pressure response[31]. This would make AT identification through cardiovascular responses difficult or even impossible. In addition, hypertension and T2D very frequently coexist, since 20% of hypertensive patients have T2D, and 80% of people with T2D are hypertensive[32]. Hypertensiveness, could also affect the hemodynamic responses during exercise, which may in turn complicate AT detection through cardiovascular responses. Sales et al. have presented the feasibility of AT identification for T2D individuals through HRV analyses[2] and Kumagai et al. identified the double product breakpoint (DPBP) in T2D individuals, but did not compared with any other anaerobic threshold identification method[23]. Thus, we hypothesized that AT could be predicted through the DPBP during exercise performed by T2D individuals, similar to healthy individuals[16]. Moreover, identification of AT through the DPBP would be relevant since the DP can provide information that correlates with myocardial oxygen consumption, which is recognized as a non-invasive indicator of cardiac overload[33, 34] as well as cardiac ischemic events including acute myocardial infarction[35]. Further, the determination of AT through the DPBP is a simple method that does not depend on the use of complex equipment such as gas analyzers, which are expensive and require the use of specialized technicians to operate them.

The validity of the DPBP in estimating the AT using a sphygmomanometer and stethoscope has not been investigated yet. Experiments have used either automated blood pressure monitor[15–17, 19, 20, 23] or a cannula inserted into the brachial artery[18]. These procedures are not accessible to most practioners because they require costly equipment as well as highly invasive procedures. In addition, to the best of our knowledge, no study has examined the DPBP as an estimate of the AT in individuals with T2D.

Thus, the purpose of this study was to verify whether or not the AT of T2D individuals can be predicted through the DP method, and to analyze the relationships between the workload (Watts), oxygen consumption (VO_2) and HR obtained by the DPBP and the ventilatory threshold (VT) methods.

SUBJECTS AND METHODS

After approval from the local human research ethics committee (*Universidade Católica de Brasília*: 011/2011), and obtaining the written informed consent of the volunteers, 11 T2D individuals (8 females), and 10 controls (7 females) were initially selected to participate in this study. Exclusion criteria for participation in this study included previous diagnosis of peripheral neuropathy or retinopathy, as well as diabetic foot ulcerations osteomioarticular complications, the endogenous use of insulin, and/or use of medicines that could have directly affected HR or BP. All the individuals were recruited at a public hospital, and all had been previously assessed using standard tests conducted by endocrinologists and cardiologists. Two participants with T2D were excluded from the analysis because it was not possible to detect their VT and/or DPBP (Table 1). Therefore, the statistical power a priori conferred on this sample (n=19) was 82% (power=0.82). The T2D individuals were receiving medical treatments of oral hypoglycemiants (*Metformin, Metformin + Glibenclamide*). The general characteristics of the volunteers are presented in Table 2.

All experimental sessions were carried out at the Laboratory of Physical Evaluation and Training (LAFIT) of the *Universidade Católica de Brasília* 2 h after volunteers eaten a standardized breakfast of a moderate glycemic index meal without any substances that could have directly affected the HR and/or the BP. The participants were given a physical evaluation including anthropometric measurements (body mass, height and body fat percentage) and then performed an incremental

Table 1. The number of cases in which the ventilatory threshold (VT) and the double product breakpoint (DPBP) were detected by all observers

Parameter	T2D (n)	ND (n)	TOTAL
Participants initially screened	11	10	21
VT detected	10	10	20
DPBP detected	9	10	19
HR primarily responsible for DPBP	1	1	2
SBP responsible for DPBP	5	4	9
Participants included in the analysis	9	10	19

T2D: individuals with type 2 diabetes; ND: individuals without T2D; VT: ventilatory threshold; DPBP: double product breakpoint; HR: heart rate; SBP: systolic blood pressure

exercise test (IT). During the IT, measurements of HR, BP and ventilatory variables were continuously monitored. To carry out the measurement of body fat percentage by bipolar bioimpedance, the individuals were told to: avoid caffeine and alcohol for 24 hours before the test; not perform physical activity or eat a heavy meal for at least 4 hours before the test; and suspend diuretic medication 24 hours before the test[36].

The IT was performed on a cycle ergometer (Monark, 828 E, Valburg/Sweden) at 60 rpm, and began one minute at zero Watt (W) load, followed by increments of 15 W every 3 minutes until voluntary exhaustion. The cardiologist of the laboratory monitored the electrocardiogram (ECG) of the volunteers throughout the test in order to identify any abnormality.

During the period before the exercise, as well as during the last 30 seconds of each stage, blood pressure (BP) was measured non-invasively by the auscultatory method using a mercury column sphygmomanometer (Tycos Instrumentos Hospitalares, São Paulo, Brazil). Expired gases were measured during the IT through a gas analyzer (Metalyzer 3B, Cortex Biophysik, Leipzig, Germany) that was previously calibrated with a 3-L syringe (flow calibration) and a standard mixed gas containing 4.9% CO_2 and 17% O_2 (gas calibration). The values of ventilation (VE) and oxygen uptake (VO_2) were recorded breath-by-breath, but, they only were analyzed every 20 s in each 3-min stage.

The ventilation (VE) kinetics during the IT stages were used to identify the occurrence of VT by two experienced researchers. This was considered to be the exercise intensity above which an over proportional increase in VE was observed in relation to increasing workload[37].

Systolic blood pressure (SBP) and HR were collected in the final minute of each stage. The DPBP was considered to be the exercise intensity at which an over proportional increase in DP was observed in relation to increasing workload. Two experienced researchers determined DPBP, and when a discrepancy between them occurred, a third researcher was consulted. All the plots were blinded, therefore the researchers did not know the identity of the subjects or the conditions of the test. It is noteworthy that the same evaluator, which did not participated in the determination of DPBP and VT, carried out all collections of BP and HR. These procedures were carried out to ensure that researchers remained 'blinded' to the analysis.

After assessing the normality and homogeneity of data through the Shapiro-Wilk and Levene's test, respectively, the data were presented as means (±) standard deviation. In order to compare the characteristics of the groups, the Student's t-test for independent samples was conducted. Between and within groups comparisons were carried out using Split-Plot ANOVA (Mixed ANOVA). When any of the dependent variables did not show sphericity in Mauchly's test, the epsilon of Greenhouse-Geisser was used to analyze the *F* statistic. Since there were only two groups, the post hoc is unable to locate the differences, therefore, it was necessary to apply parallel test, named: pairwise comparisons. Thus, the paired Student's t-test was used to compare the anaerobic threshold identification methods within groups (VT and DPBP). The Effect size within (VT and DPBP) and between groups (T2D and ND) was evaluated using Cohen's *d*[38]. Pearson's correlation coefficients were used to verify the relationships between the studied methods used to determine anaerobic threshold. For the sample size calculation, the statistical power (1-β) was used a priori, using comparison analysis applied (ANOVA for repeated measures), an effect size of f=0.35 and an alpha of 5%. Furthermore, the Bland and Altman technique was used to verify the level of agreement between the different methods[39]. A significance level of 5% ($p<0.05$) was used. All the procedures were carried out using the Statistical Package for the Social Sciences (SPSS 20.0) and G*Power (version 3.1.9.2).

RESULTS

The DPBP was identified in all 11 ND individuals and in 9 from 11 T2D individuals (81.8%), with SBP being primarily responsible for the DPBP in almost half of all cases (Table 1).

The results presented in Table 3 show no there were no significant differences between the workloads (watts), HR (bpm)

Table 2. Characteristics of the individuals with type 2 diabetes (T2D) and non-diabetic (ND) controls

	T2D (n=9)	ND (n=10)
Age (yrs)	63.2 ± 8.9	58.3 ± 7.8
Body mass (kg)	70.2 ± 14.1	72.5 ± 19.2
Height (m)	1.59 ± 0.1	1.61 ± 0.11
BMI ($kg \cdot m^{-2}$)	26.3 ± 5.0	27.1 ± 4.1
Body Fat (%)	37.4 ± 5.6	34.5 ± 7.0
HbA_{1c} (%)	6.8 ± 1.3	5.2 ± 0.2*
VO_2peak ($ml \cdot kg^{-1} \cdot min^{-1}$)	21.4 ± 3.5	22.6 ± 5.1
Maximal heart rate (bpm)	150.2 ± 24.6	155.2 ± 12.6

Data expressed as mean ± standard deviation.
T2D: individuals with type 2 diabetes; ND: individuals without T2D; BMI: body mass index; HbA_{1c}: glycated hemoglobin; *significant difference ($p<0.05$)

Table 3. Workload (watts), heart rate (bpm) and oxygen uptake ($ml \cdot kg^{-1} \cdot min^{-1}$) measurements at VT and DBPB of the T2D and ND groups

Parameter		T2D (n=9)	ND (n=10)
Workload (watts)	DPBP	45 ± 21.2	60 ± 29.2
	VT	40 ± 24.9	63 ± 30.6
Heart rate (bpm)	DPBP	124.7 ± 13.6	119.1 ± 17.4
	VT	122.1 ± 14.6	121.4 ± 19.1
VO_2 ($mL \cdot kg^{-1} \cdot min^{-1}$)	DPBP	14.6 ± 2.4	15.1 ± 2.9
	VT	14.1 ± 3.4	15.3 ± 3.6

Data expressed as mean ± standard deviation.
T2D: individuals with type 2 diabetes; ND: individuals without T2D; DPBP: double product breakpoint; VT: ventilatory threshold

and VO_2 corresponding to the AT identified by the VT and DPBP methods. Further, for the T2D group, strong and significant correlations ($p<0.01$) between workloads at VT and DBPB ($r=0.853$), HR ($r=0.714$), and VO_2 ($r=0.863$) were found. Strong and significant correlations ($p<0.001$) were also found in the ND group for all parameters investigated; they were $r=0.923$ for the workload at VT and DPBP, $r=0.881$ for HR, and $r=0.863$ for VO_2.

The Bland and Altman analyses indicate there was good agreement for the VO_2 ($L \cdot min^{-1}$) corresponding to VT and DPBP based on the low bias and narrows limits of agreement [Bias (± 95% of confidence interval)] for VT and DPBP [0.03 (0.11) $LO_2 \cdot min^{-1}$] for the T2D group, and VT and DPBP [−0.02 (0.13) $LO_2 \cdot min^{-1}$] for the ND group.

DISCUSSION

The main finding of this research is that the DPBP can be used to estimate the AT of T2D and ND individuals, since there were no significant ($p<0.05$) differences between the workloads (Watts), HR and VO_2 of the VT and DPBP methods. Furthermore, the effect size analyses also demonstrated that the visual differences of the variables mentioned above, had little (small) or no effect, according to Cohen's d[38].

From a physiological point of view, it is presumed that the DP could be a marker of AT determination, to the extent that, when performing an incremental exercise test, there is a gradual reduction in the vagal activity and consequent increase in sympathetic nervous activity. However, at a certain intensity, a complete vagal withdrawal is expected and this presents as a persistent depression of the autonomic nervous system until the end of the tests, featuring the HRV threshold[2, 40, 41]. Accordingly, there is a marked increase in sympathetic nerve activity, which results in a significant elevation of catecholamines, which is known as the catecholamines threshold[12]. The increased levels of catecholamines, in turn, result in a marked increase in BP and HR, and thus on DP, and as a result the DPBP[15–19]. Furthermore, increased levels of catecholamines also produce a significant increase in glycolytic activity[42], enabling for the identification of the glycemic and lactate thresholds[3]. This increased glycolysis also contributes to a sharp increase in CO_2 production which causes hyperventilation and results in the appearance of the VT[43].

Consequently, it is reasonable to infer that, similar to other markers (HRV, catecholamines, glucose, lactate and ventilation), the DP can also be used to determine the AT, with the advantage of it being a non-invasive and low cost method. Exercise tests involving blood collection and biochemical measures, and the use of expensive apparatus for expired gases analysis, as well as trained professionals who know protocols are high-priced, and thus inaccessible to a major portion of the T2D population.

Interestingly, although there was no significant difference of the workloads (Watts) between the groups (T2D and ND), the effect size of the difference was considered medium ($d=0.588$) for DPBP and large ($d=0.824$) for VT. From a practical point of view, it is noteworthy that the effect size is considered the main finding of a quantitative study, with the statistical significance (p) being the least important[44, 45], since the relevant point is the magnitude of differences[45].

With regard to the internal load variables (HR and VO_2), these did not present significant differences ($p>0.05$) between the groups (T2D and ND), while the effect sizes of the differences were small or even null. Additionally, intra-group differences were always null. Moreover, the fact that significant differences ($p>0.05$) were not observed between the internal load variables (HR and VO_2) of T2D and ND groups, may be partly explained by the higher cardiorespiratory capacity of the healthy individuals, as they reached an absolute external load (Watts), but with a similar cardiorespiratory responses (HR and VO_2). Additionally, another aspect that should be considered regarding the absence of significant differences between the T2D and ND groups, is that they presented quite similar characteristics (Table 2), since the only variable that was different between the groups was glycated hemoglobin (HbA_{1c}).

It is noteworthy that the statistics reveal there were strong and significant correlations between workloads (Watts), HR and VO_2, and also a good agreement in both the T2D and ND groups. This is in agreement with the study of Riley et al., who reported a strong and significant correlation between VO_2 at the lactate threshold (LT) and DPBP ($r=0.86$; $p<0.01$)[16]. Likewise Tanaka et al. also observed a strong and significant correlation between the DPBP and the LT ($r=0.90$; $p<0.01$) in a sample of 90 patients[17]. Additionally, Kumagai et al. identified the DPBP in 63 T2D individuals in a submaximal ramp test (rating of perceived exertion of 15) performed on a cycle ergometer[23]. However, it is noteworthy that in that study the DPBP was not compared with any other AT identification method.

Regarding the comparison of DPBP and VT, Brubaker et al. previously demonstrated a strong and significant correlation between the methods ($r=0.81$, $p<0.01$) in a progressive test on a treadmill, and suggested that DPBP could be a valid alternative to VT for individuals with coronary artery disease[15]. Also Omiya et al. reported a high and significant association between workloads (Watts) ($r=0.95$; $p=0.01$) of both the DPBP and VT of 15 patients with cardiovascular diseases[18].

Similarly, Hargens et al. conducted an elegant longitudinal study in order to evaluate the effect of eight weeks of aerobic training at vigorous intensity on DPBP and VT. They evaluated 7 men and 11 sedentary women, using a ramp protocol on a cycle ergometer, and observed that HR and VO_2 at baseline and at the end of the training period were similar ($p>0.05$) and showed good agreement[19]. The fact that this previous study reported an increase of DPBP after training, confirms it is a reliable and sensitive method of identifing AT adaptations to training.

One limitation of the present study was that the intensity of the maximum lactate steady state (MLSS) was not determined for comparison with the investigated protocols of DPBP and VT. The determination of MLSS is considered the gold standard

among the exercise assessment methods[1)]. Nevertheless, Denadai et al. and van Schuylenbergh indicate that this parameter is not different from the lactate threshold and VT[46–48)]. Thus, it is reasonable to infer that the methods investigated in this study, DPBP and VT, which did not differ between themselves, may also represent the MLSS intensity.

The present study demonstrated that the DPBP can be easily determined during incremental exercise in both T2D and ND controls. Additionally, the DPBP happened at exercise intensities related to the VT in both the populations studied, suggesting that DPBP can be a useful marker of exercise intensity associated with AT.

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