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Cardiopulmonary exercise test in type 2 diabetes mellitus in absence of chronic heart failure: reduced lung and heart function

Avaliação cardiopulmonar em portadores de diabetes melitus tipo 2 sem doença cardíaca: redução da função caridorespiratória

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Danilo R. Bertucci[1]
Nuno M. F. de Sousa[2]
Gabriella S. Soares[4]
Danielle P. Albano[4]
Giovanna B. Togashi[4]
Vilmar Baldissera[3,4].

[1]Universidade Estadual Paulista Júlio de Mesquita Filho
[2]Universidade Estácio de Sá
[3]Universidade Federal de São Carlos
[4]Universidade de São Paulo

ABSTRACT: Was compared exercise tolerance, respiratory and cardiovascular functions between non-diabetics and type 2 diabetics individuals (T2DM) without chronic heart failure. Thirteen normaglycemic men (non-diabetic group – NDG) and eight T2DM (diabetic group – DG) performed a cardiopulmonary exercise test (CPX) on motor treadmill (test initiated at 3 km.h-1 with an increment of 1 km.h-1 every two minutes) to evaluate respiratory function, cardiovascular parameters and exercise tolerance. Workload and oxygen uptake (O2) values at ventilatory threshold were significantly lower for DG (DG: 5.6 ± 0.5 km/h and 13.1 ± 3.8 mL.(kg.min)-1; NDG: 6.5 ± 0.5 km/h and 16.4 ± 2.8 mL.(kg.min)-1; $p < 0.05$). Peak O2 and workload were significantly lower for DG (22.7 ± 5.7 mL.(kg.min)-1;8.2 ± 0.7 km/h) when compared with NDG (30.8 ± 5.4 mL.(kg.min)-1; 11.6 ± 1.5 km/h). Oxygen uptake efficiency slope (OUES) and circulatory power were significantly lower ($p < 0.05$) in DG, although no significant alterations were found in functional capacity and ventilatory efficiency. T2DM in absence of chronic heart failure presented exercise intolerance and lower cardiorespiratory fitness. Peak circulatory power and OUES were also reduced in these individuals.

Key Words: Maximal incremental test; Ventilatory efficiency; Circulatory power; Oxygen uptake efficiency slope and maximum oxygen uptake.

RESUMO: Foi comparar a tolerância ao exercício, funções respiratória e cardiovascular entre indivíduos não diabéticos e diabéticos tipo 2 sem doenças crônicas cardíacas. Treze homens normoglicêmicos (NDG) e oito homens diabéticos tipo 2 (DG) que realizaram um teste cardiopulmonar de esforço (TCPE) em uma esteira motorizada (o teste iniciou-se em 3km.h-1 com incremento de 1km.h-1 a cada dois minutos) que avaliou a função respiratória, parâmetros cardiovasculares e tolerância ao exercício. Valores de consumo de oxigênio e intensidades na intensidade do limiar ventilatório foram significativamente menores para o DG (DG: 5,6 ± 0,5 km/h-1 e 13,1 ± 3,8 ml.(kg.min)-1; NDG: 6,5 ± 0,5 km/h-1 e 16,4 ± 2,8 ml.(kg.min)-1; $p < 0,05$). Consumo de oxigênio pico e intensidade associada foram significativamente menores para o DG (DG: 22,7 ± 5,7 ml.(kg.min)-1; 8,2 km/h-1 ± 0,7 km/h-1) quando comparado com o NDG (30,8 ± 5,4 ml.(kg.min)-1; 11,6 ± 1,5 km/h). Oxygen uptake efficiency slope (OUES) e circulatory power foram significativamente menores para o DG ($p < 0,05$) embora não foram encontradas diferenças significativas na eficiência ventilatória. Em indivíduos portadores de diabetes tipo 2, mesmo sem a presença conhecida de doenças cardiovasculares, apresentaram menores níveis de condicionamento cardiorrespiratório e tolerância ao exercício. Circulatory power pico e OUES também foram reduzidos nesses indivíduos.

Palavras-chave: Teste incremental máximo; Eficiência ventilatória; Consumo máximo de oxigênio.

Contato: Danilo Rodrigues Bertucci - danbertucci9@gmail.com

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Introdução

Individuals with type 2 diabetes mellitus (T2DM) have poor cardiorespiratory fitness (CF) when compared with non-diabetic[1] and their overall morbidity is significantly increased when associated with heart failure[2-4]. Furthermore, poor glycemic control is associated with increased risk of heart failure[5,6]. At the lungs, alveolar–capillary membrane becomes a target structure of coexisting diseases. Left ventricular dysfunction causes a hydrostatic stress on the membrane[7], and diabetes alters alveolar and pulmonary capillary basal laminae[8], which results in synergistic depression on membrane conductance and gas exchange[9]. These alterations, in both heart failure and respiratory function, directly influence peak oxygen uptake ($\dot{V}O_2$peak) and anaerobic threshold. Kunitomi *et al.*[10] and Sales *et al*.[11] evidenced that diabetic patients had lower $\dot{V}O_2$peak, $\dot{V}O_2$ at anaerobic threshold and work rate associated with these parameters when compared with healthy men.

Unfortunately, mild alterations related to abnormal pulmonary function are generally silent at rest, 60% of diabetic adults have an abnormal pulmonary function, because the impairment in gas transfer, that may evidence a lower $\dot{V}O_2$peak values[1–6]. In this direction, evaluating metabolic, ventilatory and hemodynamic parameters during maximal exercise foretells important diagnostic and prognostic information[16-18]. This occurs at a cardiopulmonary exercise testing (CPX), which is the gold standard for non-invasive assessments of cardiopulmonary parameters and provides valuable information in different populations related to respiratory function[16,19]. Among ventilatory parameters, $\dot{V}O_2$peak and ventilation/carbon dioxide production ($\dot{V}E/\dot{V}CO_2$) slope are common predictors for overall mortality or stratification risk. These parameters, assessed in a simple way through a CPX performed in a physician's office, are often associated with cardiovascular and respiratory diseases, especially with chronic heart failure[20-22].

From these considerations, some pulmonary mechanisms involved in exercise intolerance in chronic heart failure[23] could explain impairment lung function and exercise capacity in patients with T2DM[9]. However, overventilation and hyperglycemia during physical exertion, which are potentiated with diabetes[9], could precipitate in a reduction of respiratory and cardiovascular functions, even in absence of chronic heart failure.

Thus, the aim of the present study was to compare exercise tolerance, respiratory and cardiovascular functions between non-diabetics and T2DM without chronic heart failure by a simple and non-invasive analysis of a CPX report. We hypothesized that the diabetic group will present exercise intolerance and reduced lung and heart functions.

Materials and methods

Participants

This study included 21 sedentary men. Thirteen normaglycemic (non-diabetic group – NDG) and eight type 2 diabetic men (diabetic group – DG) diagnosed through glycated hemoglobin (HbA_{1C}) > 6.5% and fasting plasma glucose > 126 mg/dL, according to recommendations of the American Diabetes Association and American College of Sports Medicine[24,25]. DG participants were recruited by phone from a list that was released by the *Unidade de Saúde Escola* (USE) at Federal University of Sao Carlos. NDG participants were employees at Sao Paulo State University and were contacted by e-mail available from the University's nursery section.

Clinical examination was performed by a physician (cardiologist) before the beginning of the present study. The examination consisted of anamnesis and 12-lead electrocardiography at rest. Blood analysis was used to determine fasting glucose, glycosylated hemoglobin, triglycerides, total cholesterol and low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Participants with resting blood pressure values > 160/100 mmHg, history of cardiovascular events, changes in cardiac function detect by electrocardiogram or pulmonary function detected by spirometry, retinopathy, nephropathy, microalbuminuria and osteartícular limitation, previously identified by a physician[24], were not included. In DG, six participants were diagnosis with systemic arterial hypertension and three with coronary artery disease.

All procedures as well as risks and benefits were explained to each participant and they signed a written informed consent, which was approved by the institutional Human Subject Review Board (protocol number: 0042011). The experimental protocol was conducted in accordance to the national health council for humans' experiments by resolution number 466-12/12.

Experimental design

After clinical examination, participants performed three visits to the laboratory: 1) interview and application of international physical activity questionnaire (IPAQ) short version; anthropometric, hemodynamic and biochemical measurements; 2) familiarization with the equipment and protocol; 3) CPX to evaluate respiratory function, cardiovascular parameters and exercise tolerance. Visits were separated by at least 48 hours and maximum of one week. Subjects were instructed not to perform strenuous exercise or ingest alcoholic and/or caffeinated beverages within 24 hours before each visit.

Anthropometric and hemodynamic evaluations

Body mass and composition were determined using a tetra polar bioelectric impedance system with electrodes in contact with soles and heels of both feet and hands (Tanita BC-558 Ironman Segmental Body Composition Monitor bioelectrical impedance scale). The measurements were performed in a quiet environment after a 12 h overnight fast, with subjects in standing position using light clothes, without shoes.

Blood pressure assessment were conducted in accordance with the VII Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines[26], which recommends a seated position with uncrossed legs, feet flat on the floor, and left arm supported at heart level. Blood pressure was measured after 10 min of rest with a calibrated automated blood pressure device (G-TECH® BP3AA1-H, Genexel Medical Instruments, South Korea).

Rest biochemical analysis

Approximately 5 ml blood was drawn from antecubital vein by venous puncture and allocated in a EDTA tube. High Performance Liquid Chromatography technique was used to analyze HbA_{1C}. Total cholesterol, triglycerides and fasting plasma glucose were analyzed by spectrophotometry.

Cardiopulmonary exercise testing

The CPX was performed on motor treadmill at 3 km^{-1} with an increment of 1 km/h^{-1} every two minutes, the treadmill grade remained in 0% during all procedure. The protocol continued until the volunteer reached the volitional fatigue or leg discomfort. Ventilatory parameters were collected by a medium pneumotachometer (6 – 120 L/min) and continuously measured by a previously calibrated gas analyzer (VO2000, Medgraphics, St. Paul, Minnesota, USA). The gas analyzer was calibrated accordingly to the fabricant´s guidelines.

Ventilatory, metabolic and cardiovascular measures

The following data were assessed on 20 seconds average: $\dot{V}O_2$ and carbon dioxide production ($\dot{V}CO_2$) at standard temperature and pressure, containing no water vapour (STPD) and the minute ventilation ($\dot{V}E$) at body temperature and ambient pressure, saturated with water vapour (BTPS).

Peak $\dot{V}O_2$ was the highest $\dot{V}O_2$ value during the exercise test and peak workload was the running velocity elicited at peak $\dot{V}O_2$. Peak respiratory exchange ratio (RER) was the average of 20-s $\dot{V}CO_2$ divided by $\dot{V}O_2$. O_2 pulse (mL/beat) was determined dividing peak $\dot{V}O_2$ (mL/min) by maximal HR (bpm). $\dot{V}O_2$ and workload at ventilatory threshold (VT) were measured by V-slope method[27]. Resting VE, $\dot{V}O_2$ and RER were expressed as a 1-min resting averaged value.

Ventilatory efficiency was measured by plotting $\dot{V}E$ against $\dot{V}CO_2$ and during exercise is represented by the slope of all $\dot{V}E/\dot{V}CO_2$ values during CPX excluding nonlinear portion of this relationship after VT[28]. Oxygen uptake efficiency slope (OUES), an index that measures cardiorespiratory functional reserve, was calculated using log-transformation (base 10) of $\dot{V}E$ by $\dot{V}O_2$; both variables, log$\dot{V}E$ and $\dot{V}O_2$, used to calculate the OUES were in L/min, as suggested by Sperling *et al.*[29] and Baba *et al.*[30]. Circulatory power was defined as the product of peak $\dot{V}O_2$ and peak systolic blood pressure[31]. Ventilatory power was defined as peak systolic blood pressure divided by the VE/VCO_2 slope[32].

Blood samples (25 µL) were collected from the earlobe at rest and immediately after CPX for blood lactate concentration (BLC) analysis. Blood samples were collected in heparinized capillaries previously calibrated[33] and stored in Eppendorf® tubes with 50-µL sodium fluoride 1%. BLC was analyzed using electroenzymatic method with a lactate analyzer (1500 Sport; Yellow Springs Instruments Inc., Yellow Springs, OH, USA). Heart rate was measured at rest and during CPX using a heart rate monitor (Polar® Si 810, Kemple, Finland). Predicted maximal heart rate was determined by the equation 220 – age. Blood pressure was obtained immediately at the end of CPX.

Table 1. Baseline anthropometric, hemodynamic and biochemical characteristics of diabetic (DG) and non-diabetic (NDG) groups (mean ± SD).

	NDG	DG
Age, years	51.5 ± 5.8	55.4 ± 7.0
Diabetes time, years	-	6,0 ± 4.3
Height, cm	172.3 ± 7.3	170.0 ± 7.8
Body mass, kg	80.8 ± 11.7	92.8 ± 9.4*
Body mass index, kg/m^2	27.2 ± 3.2	32.2 ± 3.2*
HbA1c, %	5.19 ± 0.48	9.35 ± 2.14*
Fasting glucose, mg/dL	97.8 ± 18.2	191.9 ± 55.1*
Total cholesterol, mg/dL	223.5 ± 48.1	206.1 ± 34.3
Triglycerides, mg/dL	145.4 ± 54	192.1 ± 86.9
Fructosamine, µmol/L	-	276.5 ± 69.6
Resting HR, bpm	72.7 ± 8.6	78.7 ± 11.1
Resting SBP, mmHg	116.9 ± 12.8	135.7 ± 16.9*
Resting DBP, mmHg	74.9 ± 7.2	82.5 ± 8.9*

HbA1c, glycated hemoglobin; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; * $p < 0.05$ for NDG.

Statistical analysis

Data were expressed as mean ± standard deviation (SD). Shapiro–Wilk's normality test was used to test data normal distribution. The variables analyzed in the study presented normal distribution. Independent-samples t-test was used to compare the differences between DG and NDG. Significance was assumed when $p \leq 0.05$ and SPSS version 20.0 (Somers, NY, USA) software was used.

Results

Anthropometric, hemodynamic and biochemical characteristics are summarized in table 1. Baseline fasting glucose, HbA1c, blood pressure, BMI and weight were significantly higher ($p < 0.05$) for DG.

Table 2 shows that DG had significantly lower resting $\dot{V}O_2$ values and higher baseline BLC. Workload and $\dot{V}O_2$ values at ventilatory threshold and peak exercise were significantly lower) for DG. Mean cardiopulmonary values indicate that groups had preserved functional capacity and ventilatory efficiency, however, OUES and circulatory power were significantly lower in DG.

Table 2. Cardiopulmonary exercise test parameters in diabetic (DG) and non-diabetic (NDG) groups (mean ± SD).

	NDG	DG
Rest		
VE, L/min	7.3 ± 2.7	6.1 ± 2.9
VO_2, mL.(kg.min)$^{-1}$	3.3 ± 1.6	2.0 ± 0.8*
RER	0.96 ± 0.19	1.03 ± 0.11
Lactate, mmol/L	1.4 ± 0.6	2.2 ± 0.6*
Ventilatory threshold		
Workload, km/h	6.5 ± 0.5	5.6 ± 0.5*
VO2, mL.(kg.min)$^{-1}$	16.4 ± 2.8	13.1 ± 3.8*
%VO2 peak	53.5 ± 7.4	60.3 ± 18.5
Peak		
Heart rate, bpm	164.7 ± 10.5	151.4 ± 21.0
Predcted maximal heart rate, %	98.1 ± 6.1	90.7 ± 10.3
SBP, mmHg	173.9 ± 25.5	183.7 ± 20.7
DBP, mmHg	75.7 ± 9.9	73.7 ± 13.0
Workload, km/h	11.6 ± 1.5	8.2 ± 0.7*
VE, L/min	63.1 ± 11.9	63.2 ± 16.2
VO_2, mL.(kg.min)$^{-1}$	30.8 ± 5.4	22.7 ± 5.7*
RER	1.20 ± 0.11	1.34 ± 0.08*
O_2 pulse, mL/beats	14.6 ± 2.3	15.1 ± 0.7
Lactate, mmol/L	7.2 ± 2.1	7.1 ± 1.5
VE/VCO_2 slope	17.5 ± 1.0	18.7 ± 2.9
OUES	2.67 ± 0.48	2.12 ± 0.50*
Circulatory power, mmHg.mL.(kg.min)$^{-1}$	5313 ± 967	4105 ± 913*
Ventilatory power, mmHg	3044 ± 518	3345 ± 766

VE, minute ventilation; VO2, oxygen uptake; RER, respiratory exchange ratio; SBP, systolicblood pressure; DBP, diastolic blood pressure; OUES, oxygen uptale efficiency slope; * $p < 0.05$ for NDG.

Discussion

In the present study, we examined the differences in respiratory efficiency and exercise tolerance between non-diabetic and diabetic patients in the absence of chronic heart failure. At best, our results confirmed our initial hypothesis that DG presented lower exercise tolerance than NDG. On the other hand, respiratory function was preserved in T2DM patients in absence of chronic heart failure, despite reduced OUES and circulatory power than NDG.

Lower peak $\dot{V}O_2$ and exercise tolerance for DG demonstrated a common feature related to T2DM that is poor cardiorespiratory fitness and exercise tolerance[1]. The values for $\dot{V}O_2$peak and anaerobic threshold correspond closely to patients with T2DM described in other studies[12,34]. Thus, even in an asymptomatic disease with few years, it seems that the cardiorespiratory system already has a gradual deterioration that can be detected by a simple CPX test. Evidences seem to indicate that diabetes and elevated blood glucose constitute important comorbidities with impact on lung function[7-9], that result in restrictive alterations[35]. Studies have demonstrated that rest pulmonary function tests are significantly decreased in subjects with T2DM in comparison to healthy control groups[36-38] and this might be the result of direct exposure to elevated blood glucose[39,40]. In this context, Davis *et al.*[41] proposed that reduced lung volume and airflow limitation might be considered as chronic complications of T2DM. Abnormal glycosylation led an increase on connective tissue in lungs, therefore, another possible mechanism to diabetic patient show a poor pulmonary diagnosis is related with insulin resistance, that may decrease respiratory muscle strength and affect all respiration process[42]. These alterations have an impact on exercise capacity and quality of life across functional stages of airflow limitation[43]. Interestingly, our study

shows that even in T2DM patients in absence of chronic heart failure and preserved rest pulmonary function, CPX was able to detected reductions in exercise capacity and respiratory efficiency. Although DG has consulted a physician before the study, we couldn't exclude the possibility of undiagnosed coronary or peripheral artery disease that may compromise exercise tolerance. Further studies should consider coronary or peripheral artery disease impact on exercise tolerance in TD2M.

CPX is a specialized subtype of exercise testing that provides a more accurate and objective measure of cardiorespiratory fitness[17]. Once largely under the domain of the physiologist or specialized center, CPX currently has the potential to be used for a wide spectrum of clinical applications, which includes ventilatory efficiency and risk stratification for respiratory complications[44, 45]. In this research, besides the traditional poor cardiorespiratory fitness and exercise intolerance, CPX was able to detect reduced OUES and circulatory power in T2DM patients in absence of chronic heart failure when compared to NDG.

Thus, we recommend that CPX for T2DM patients provided not only information about cardiorespiratory fitness and exercise intolerance but also respiratory efficiency parameters, such as $\dot{V}E/\dot{V}CO_2$ slope, OUES, circulatory and ventilatory power. Peak $\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ slope are currently the most studied CPX variables and both demonstrate strong independent prognosis value of cardiovascular risk, however, these parameters are applied to patients with heart failure[17,46]. When CPX is performed with T2DM patients in absence of chronic heart failure, even with reduced peak VO_2 compared to non-diabetic subjects[1], cardiorespiratory fitness can be misled with a sedentary lifestyle. Furthermore, an abnormally high $\dot{V}E/\dot{V}CO_2$ slope is associated with a poor prognosis when low peak $\dot{V}O_2$ values (< 18 mL.(kg. min)$^{-1}$) were reported. As we presented in this study, $\dot{V}E/\dot{V}CO_2$ slope for T2DM patients was far from cutoff points to predict high risk of cardiac events and presented no difference from non-diabetic subjects. Thus, it's interesting to analyze other respiratory parameters to evaluate and detect possible differences that originates from T2DM and not from sedentary lifestyle.

In attempt to avoid supra cited effects on maximal capacity or exercise intolerance, OUES was developed to analyze respiratory efficiency and is mainly applied in cardiac patients[47]. In this research, T2DM presented lower OUES than non-diabetics and also demonstrated a lower increase in $\dot{V}O_2$ in response to a given $\dot{V}E$. In other words, oxygen extraction at the lungs and its distribution through the body is impaired in T2DM. Based on physiological explanation of OUES, it seems that even in T2DM in absence of chronic heart failure perfusion to the lungs are affected – increase in physiologic pulmonary dead space and carbon dioxide production is increased – metabolic acidosis. Indeed, high BLC at rest observed in DG can be indicative of metabolic acidosis observed in T2DM patients. Finally, circulatory power, considered another predictor of cardiovascular outcome in patients with chronic heart failure, was analyzed in the present study[31]. Our results indicate that peak circulatory power was able to detect differences between DG and NDG, even in absence of chronic heart failure. T2DM in absence of chronic heart failure had a reduced circulatory power when compared to ND, indicating an increased cardiovascular risk. Cohen-Solal *et al*.[31] state that peak circulatory power should not be viewed as only a perfect surrogate of cardiac power, but as a new global index that incorporates, besides $A\dot{V}O_2$ difference, heart rate, stroke volume and blood pressure responses, all parameters whose prognostic value has been demonstrated.

Unfortunately, both peak circulatory power and OUES are widely studied only in chronic heart failure patients. We are unaware of any previous investigation, which has compared peak circulatory power or OUES on diabetic and non-diabetic population. Thus, peak circulatory power and OUES measures presented in this study doesn't permit to establish the degree of ventilatory or cardiovascular impairment neither a prognosis prediction. This research was only able to detect differences in CPX variables between a sample of T2DM and non-diabetic individuals. Since the difference were identified in a small sample and can be physiologically explained, we recommend a large-scale study of these variables in T2DM in absence of chronic heart failure. It is possible that large-scale researches can identify cutoff points for OUES and circulatory power for cardiovascular prognosis.

Conclusions

In conclusion, T2DM without chronic heart failure presented exercise intolerance and lower cardiorespiratory fitness demonstrated by lower workload and $\dot{V}O_2$ at ventilatory threshold and lower peak workload and peak $\dot{V}O_2$.

Peak circulatory power and OUES were also reduced in T2DM, showing impairment on lung and heart function in T2DM absent of chronic heart failure. It can be assessed non-invasively through a maximum CPX test. Future studies should explore OUES and peak circulatory power in T2DM patients in absence of chronic heart failure.

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