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ORIGINAL PAPER

Circulatory and ventilatory power markers in patients with diabetes mellitus – influence of glycemic control

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ABSTRACT

Introduction and aim. Cardiorespiratory function has been shown to be impaired in individuals with type 2 diabetes mellitus (T2DM). Some deficiencies in cardiopulmonary exercise test (CPET)-derived variables are known, however, the influence of glycemic control on cardiovascular integrity indices as circulatory power (CP) and ventilatory power (VP), deserve to be instigated. The aim was to investigate the influence of glycemic control on CP and VP indices in T2DM.

Material and methods. T2DM individuals of both sexes aged between 40 and 64 years were allocated into two groups: Good glycemic control (GGC, n=11; HbA1c≤7%) and insufficient glycemic control (IGC, n=26; HbA1c>7%). All participants underwent a CPET on a treadmill using a gas analyzer and a laboratory blood test. CP values were obtained by the product of peak of oxygen uptake and systolic blood pressure (SBP) and VP by dividing SBP by the ventilatory efficiency (VE/VCO2 slope). The level of significance was set at $p<0.05$.

Results. No baseline differences were found between the groups, except for the expected fasting glucose and glycated hemoglobin. No differences were found between GGC and IGC groups for CP (4756.05±1061.67 and 4434.15±1247.83 mmHg.ml.kg^{-1}min^{-1}, p=0.460) and VP (5.85±1.08 and 5.86±1.31 mmHg, p=0.978), respectively.

Conclusion. CP and VP were similar in individuals with T2DM regardless of glycemic control. Predictive ability of these variables in health outcomes deserves to be further investigated in T2DM.

Keywords. cardiopulmonary exercise test, glycemic control, type 2 diabetes mellitus

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by persistent hyperglycemia, resulting from a deficiency in the production of insulin by the pancreas, in its action, or both mechanisms.[1] The number of people diagnosed with DM has increased in several countries. In 2019, the worldwide prevalence of DM was 463 million people, with a forecast of reaching 700 million in 2045.[1]

One aspect of health impairment in patients diagnosed with DM type 2 (T2DM), contributing to a higher risk of cardiovascular disease (CVD), is related to the inability to perform activities of daily living when compared to individuals without the disease[2] and low cardiorespiratory functional capacity, that can be accessed through oxygen uptake (VO2), as studies show a strong inverse association between cardiorespiratory function-

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al capacity and diabetes, which is a significant risk factor for mortality in this population.[3-5]

Cardiopulmonary exercise test (CPET) is a non-invasive procedure aimed to assess patient's functional capacity being considered the gold standard for aerobic capacity or cardiorespiratory and metabolic performance assessment.[6] Peak oxygen consumption ($VO2_{PEAK}$) is the most representative parameter of cardiorespiratory physical fitness, whose strong association with aerobic physical performance certifies it as a tool for the prescription of aerobic physical training.[7] However, for some groups of patients, such as diabetic patients who have very low $VO2_{PEAK}$ ranges, this variable may lose its prognostic value a little, giving way to other important variables also obtained by CPET.

Circulatory power (CP) and ventilatory power (VP) has been demonstrated important marker of individual's cardiovascular integrity level.[8] According to the authors Forman et al, low CP values indicate a worse prognosis of the disease, while high VP values indicate a better prognosis.[9] CP assesses the central and peripheral components of cardiac work, being defined as a product of peak $VO2_{PEAK}$ and peak systolic blood pressure (SBP_{PEAK}) while the VP index combines the assessment of the hemodynamic system with ventilatory efficiency during exercise, being defined by the division of PAS_{PEAK} by VE/VCO2 slope representing the ventilatory efficiency for the production of carbon dioxide.[10,11] For some variables, there are already known and tabulated values, among the most used is the American Heart Association functional classification table published in 1972, which is based on the $VO2_{PEAK}$ obtained in a CPET. Regarding the variables that will be addressed in this study, Mezzani presents a table with CP normality values for healthy people, however, there are still no comparative values with the diabetic population.[12] Regarding VP, we did not find tables with normal values in the literature.

We can also consider glycemic control as an important factor for DM control. Adequate glycemic control delays the onset and progression of microvascular complications, in addition to reducing the risk of cardiovascular events by 42% and by 57% of non-fatal myocardial infarction, stroke, and death.[13] When intensified, glycemic control can prevent and/or delay the onset of chronic DM complications, and the glycemic index and glycemic load are useful factors to predict the glycemic response to foods.[14] Also, it is already know the impact of poor glycemic control in the aerobic capacity demonstrated by low VO2PEAK and workload achieved in CPET.[15]

In this way, glycated hemoglobin (HbA1c) reflects the average concentration of glucose in the blood in recent weeks, instead of the concentration of glucose in the blood at that moment representing the percentage of hemoglobin that is bound to glucose.[16] HbA1c levels above 7% indicate poor glycemic control and are associated with a progressively higher risk of chronic complications, hence the current concept of diabetes mellitus treatment defined by the Brazilian Diabetes Society (SBD) stipulated the value of 6.5% as the upper limit of the acceptable value for a patient with well-controlled DM.[17,18]

Aim

This study aimed to explore the influence of glycemic control on CP and VP indices in T2DM patients. We hypothesize that the worst glycemic profile would translate into a worse PC and VP.

Material and methods

This was a cross-sectional, observational study, followed by STROBE statement and was developed at the Laboratory of Cardiopulmonary Physiotherapy (LACAP) at the Federal University of São Carlos (UFSCar).

Selection of participants and ethical aspects

The study included individuals of both sexes with a previous diagnosis of T2DM[19] and aged between 40 and 64 years, residents in the city of São Carlos - São Paulo, Brazil, who were allocated into two groups: good glycemic control group (GGC) and insufficient glycemic control (IGC) according to value for dividing the groups at 7% HbA1c.[17] The study did not include smokers, alcoholics, or illicit drug users, participants who presented: changes in the electrocardiogram [ischemia, overloads, severe arrhythmias (such as ventricular tachycardia) and conduction disorders], both at rest and during the clinical physical exercise test, participants with neurological and orthopedic disorders, participants who did not have sufficient level of understanding to understand the routine of the protocols.

The recruitment of participants was carried out through dissemination in electronic and printed media, and patients registered in the Basic Health Units. After identifying the eligible participants, they were invited to participate in the study and after their acceptance, they performed all the assessments described below.

Participants were also informed and oriented about the procedures they would be submitted to, and the methods used in this study and the non-invasive nature of the experiments. Information was also provided to participants about the confidentiality of data collected during the study and about the preservation of their identities. After clarifying all the doubts raised by the participants and freely accepting to participate in the research, all signed an informed consent form, following the norms of the National Health Council (resolution 466/2012).

Sample characterization

All participants underwent an anamnesis to obtain personal data such as full name, address, age, body mass, height, daily life, and eating habits. Participants were also asked about medications in use, family history, and history.

A laboratory blood tests were performed at Medical Laboratory Dr. Maricondi Sao Carlos – Brazil, Biochemical analyses, including fasting serum lipids (total cholesterol and fractions and triglyceride), glucose profile (glycemia and fasting insulin Homeostasis Model Assessment index – HOMA and HbA1c and complete blood count. Samples were drawn between 7:00 a.m. and 10:00 a.m. and participants were instructed to fast for 8 to 12 hours.

Cardiopulmonary exercise test (CPET)

CPET was performed in the presence of a cardiologist, in order to assess the aerobic capacity of the participants as well as to obtain the variables of interest for this study ($VO2_{PEAK}$ and VE/VCO2 slope) in addition, systolic blood pressure was monitored by the auscultatory method using a sphygmomanometer (Tycos/Bic, Brazil) and a stethoscope (Littmann® Classic III, Brazil). CPET, considered the gold standard for aerobic capacity assessment, was performed on a treadmill (Super ATL, Porto Alegre, Rio Grande do Sul, Brazil) applying the Bruce steps incrementally. There was an increase in speed and inclination every 3 minutes. To analyze the ergospirometric variables, an Oxycon Mobile® gas analyzer (Mijnhardt/Jäger, Würzburg, Germany) was used. Volunteers were encouraged to perform the test until exhaustion and the criteria for test interruption were those described by Balady.[20]

Operationalization of variables

During CPET, the following variables were collected for analysis: $VO2_{PEAK}$, peak carbon dioxide production ($VCO2_{PEAK}$), respiratory exchange rate (RER) were defined as the mean of the last 30 seconds of exercise.[21] Blood pressure was measured at the end of each stage of the test and at the time of peak exercise. The VE/VCO2 slope was calculated from the beginning to the peak of the exercise and the value considered to be VE/VCO2 slope was obtained through linear regression between these variables. CP values were obtained by the product of $VO2_{PEAK}$ by SBP_{PEAK}[22] and VP by dividing the SBP_{PEAK} values by the VE/VCO2 slope[10] (Fig. 1).

Statistical analysis

For statistical analysis, the Sigma Plot 11.0 software will be used (Systat, USA, 2011). The normality of data distribution will be verified by the Shapiro-Wilk test. For comparison between groups according to population characteristics, laboratory tests, and CP and VP indices obtained in CPET, t-test will be used for data with normal distribution and Mann-Whitney test for non-normal distribution. Data are presented as mean ± standard deviation for data with normal distribution and median and interquartile range for data with non-normal distribution.

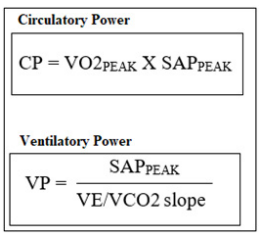

Fig. 1. Circulatory and ventilatory power equation[a]

[a] CP – circulatory power, SAP_{PEAK} – peak of systolic arterial pressure, VE/VCO2 slope – relationship between minute ventilation and carbon dioxide production, $VO2_{PEAK}$ – oxygen uptake, VP – ventilatory power

To assess the relationship between glycemic control and, VP and CP Pearson correlation test was used. Classification to correlation coefficient was the proposed by MUNRO, 2001 with a small correlation being considered: values from 0 to 0.25; low from 0.26 to 0.49; moderate from 0.50 to 0.69; high from 0.70 to 0.89; and very high from 0.90 to 1.00.[23] The level of significance was set at $p<0.05$.

Results

Thirty-seven patients diagnosed with T2DM participated in this study and were divided into two groups (GGC, n=11 and IGC, n=26). Baseline characteristics of the groups are described in table 1. No baseline differences were found between the two groups, except for the expected fasting glucose and glycated hemoglobin.

Regarding the cardiovascular parameters during cardiopulmonary the results are described in table 2.

In the interest variables (CP and VP), no differences were found between the studied groups and the results are described in table 2 and figure 2A and 2B. Furthermore, there was no relationship between the main variables and glycemic control, either within each group or total number of participants (Table 3).

Discussion

The present study aimed to investigate the influence of glycemic control on aerobic functional capacity through circulatory power and ventilatory power in patients diagnosed with T2DM. After the patients were submitted to the cardiorespiratory exercise test, we can consider that, for the studied sample, it was not possible to identify differences between the variables. The initial hypothesis of this study was based on the premise that patients

Table 1. Sample characterization

	GGC (n=11)	IGC (n=26)	p	TOTAL (n=37)
Age (years)	53 ± 8	54 ± 8	0.69	54 ± 8.26
Gender (M/F)	7M/4F	19M/7F		26M/11F
Body mass (kg)	84.06 ± 14.95	87.10±15.46	0.58	86.20 ± 5.17
Height (m)	1.7 ± 0.13	1.72 ± 0.1	0.68	1.72 ± 0.11
BMI (kg/m^2)	28.47 (25.4–30.89)	29.61 (25.74–30.96)	0.79	29.1 ± 4.7
Fasting glucose (mg/dl)	125 (115.25–129.75)	147.5 (127–170)	**0.01**	148 ± 50.32
Glycated hemoglobin (%)	5.87 ± 1.16	8.98 ± 1.53	**<0.001**	8.06 ± 2.02
Total cholesterol (mg/dl)	172.18 ± 44.47	184.59±45.56	0.45	180.9 ± 44.99
HDL (mg/dl)	44 (38–55)	42.5 (32–50.6)	0.22	44.93 ± 14.69
LDL (mg/dl)	94.72 ± 44.73	112.46 ± 39.93	0.24	105.5 ±4 2.08
VLDL (mg/dl)	27.09 ± 12.35	33.92 ± 14.58	0.19	31.77 ±14.11
Triglycerides (mg/dl)	114 (82–184.25)	193 (116–232)	0.13	181.98 ± 122
Diabetes time (years)	2 (1–5.5)	7 (4–10)	**0.03**	6.65 ± 5.6
Hypertension, n (%)	4 (36)	6 (23)	0.44	10 (27)
Obesity, n (%)	4 (36)	11 (38)	0.78	15 (41)

[a] Data presented as mean ± SD and median (quartile 1 – quartile 3), BMI – body mass index, GGC – good glycemic control group, HDL – high-density lipoprotein, IGC – insufficient glycemic control group, LDL – low-density lipoprotein, VLDL – very-low-density lipoprotein

Table 2. Cardiovascular parameters during cardiopulmonary testing[a]

	GGC (n=11)	IGC (n=26)	p	TOTAL (n=37)
Rest				
HR_{REST} (bpm)	76 ± 11	82 ± 11	0.13	80.84 ± 11.05
SBP_{REST} (mmHg)	130 (111.5–130)	130 (120–140)	0.21	131.68 ± 17.16
DBP_{REST} (mmHg)	80 (72.5–90)	80 (80–90)	0.66	81.78 ± 8.42
Peak exercise				
VO_{2Peak} (ml/kg/min)	23.4 (19.57–27.02)	21.4 (19.3–25)	0.33	22.51 ± 4.46
VE/VCO2 slope	35.52 (32.82–38.88)	34.3 1(31.8–37.11)	0.58	35.27 ± 6.32
OUES	1.94 ± 0.51	1.84 ± 0.42	0.54	1.87 ± 0.45
HR_{PEAK} (bpm)	163 ± 18	155 ± 20	0.28	158.13 ± 19.25
% HR_{MAX}	97.77 ± 8.92	95.35 ± 10.44	0.47	96.13 ± 9.96
SBP_{PEAK} (mmHg)	201 ± 19	201 ± 30	0.98	201.08 ± 26.93
DBP_{PEAK} (mmHg)	90 (90–107.5)	100 (90–110)	0.59	98.35 ± 12.36
RER	1.13 (1.08–1.23)	1.12 (1.07–1.20)	0.48	1.14 ± 0.1
VP (mmHg)	5.85 ± 1.08	5.86 ± 1.31	0.98	5.86 ± 1.24
CP (mmHg.ml.kg^{-1}min^{-1})	4756.05 ± 1061.67	4434.15 ± 1247.83	0.46	4529.85 ± 1190.23

[a] CP – circulatory power, DBP_{PEAK} – peak diastolic blood pressure, DBP_{REST} – resting diastolic blood pressure, GGC – good glycemic control group, HR_{PEAK} – peak heart rate, HR_{REST} – resting heart rate, IGC – insufficient glycemic control group, RER – respiratory exchange ratio, SBP_{PEAK} – peak systolic blood pressure, SBP_{REST} – resting systolic blood pressure, VE/VCO2 slope – ventilatory efficiency index slope of the ventilatory equivalent of carbon dioxide, VO_{2PEAK} – peak oxygen uptake, VP – ventilatory power

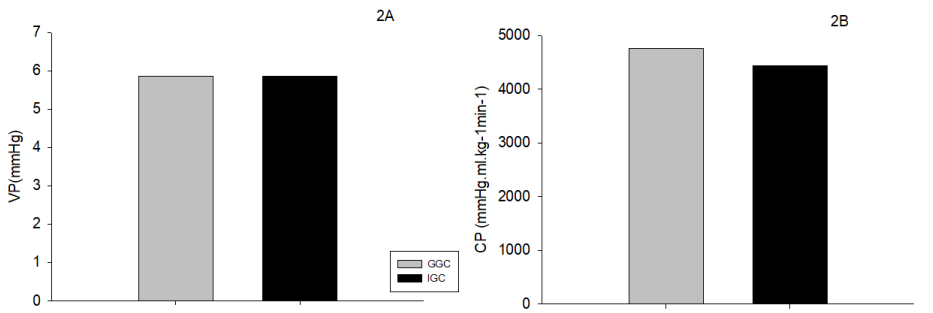

Fig. 2. Circulatory and ventilatory powers comparation [a]

[a] CP – circulatory power, GGC – good glycemic control, IGC – insufficient glycemic control, VP – ventilatory power

with insufficient glycemic control would have lower CP and VP values when compared to patients with good glycemic control, however, when analyzing the results of both groups, the variables presented values without significant differences, which was not expected.

Table 3. Correlation coefficient analysis between glycemic control (HbA1c) and ventilatory power and circulatory power[a]

	r	p
IGC		
VP	-0.205	0.314
CP	0.045	0.825
GGC		
VP	-0.398	0.225
CP	-0.443	0.172
TOTAL		
VP	-0.167	0.322
CP	-0.128	0.451

[a] CP – circulatory power, GGC – good glycemic control group, IGC – insufficient glycemic control group, VP – ventilatory power

The literature suggests that the increase in HbA1c has been shown to be an independent predictor of cardiovascular disease in adult patients with T2DM.[24] Complications, both macro and microvascular, including diabetic neuropathy, are strongly related to the increase in HbA1c[17] and among the symptoms related to this type of neuropathy is exercise intolerance[25] which leads to low adherence to physical exercise programs resulting in a reduction in cardiorespiratory capacity assessed by peak oxygen consumption when compared to a control group.[26] In this context, our findings corroborate those found in the literature, since the patients included in this study also had reduced aerobic functional capacity according to the American Heart Association.[27]

In this way, insufficient glycemic control can compromise physical fitness accessed by maximal oxygen uptake as confirmed by Niranjen et al. when comparing healthy patients with controlled and uncontrolled diabetic patients.[28] We expected to find the same differences comparing CP and VP since mechanisms such as autonomic control and compromised pulmonary responses and arterial stiffness may affect these variables as well as physical fitness.[15,29]

Regarding CP and VP, we have not yet found reference values for the T2DM population that can provide us with comparative information to our findings, however, one study compared patients with coronary artery disease with healthy individuals finding, in this population, higher values for the two variables.[9] Comparing the values found in our study with those described by Castello-Simões, we can say that the T2DM population has CP and VP values lower than the healthy population.[9] Likewise, Mezzani describes that CP is an interesting parameter provided by the cardiopulmonary exercise test capable of non-invasively evaluating the systolic function of the left ventricle during incremental exercise, in this study the author brings values of reference for the healthy population ranging from 5680 to 7050 $mmHg.ml.kg^{-1}min^{-1}$.[12] Thus, the patients involved in this study had lower CP values compared to the reference values mentioned.

We had the hypothesis of this study that T2DM patients who were part of the group with worse glycemic control would have worse values of CP and VP, due to all the adverse effects caused by this lack of control, which has already been described above, however, we did not find differences between the groups studied. We believe that regardless the glycemic control, low aerobic functional capacity of T2DM patients in both groups may have reflected in the values of CP and VP since VO-2PEAK presents a significant correlation with the studied variables.

Our study also had some limitations. First, the sample size was relatively small, especially for the group with good glycemic control. Second, the lack of a control group with apparently healthy subjects to compare CP and VP, since there are no reference values for these variables for the T2DM population.

As clinical importance, we can highlight that given the already known importance of glycemic control in several complications in T2DM, this study intended raise awareness regarding the disease control, however, although we did not observe a direct influence on the PC and PV indices, sample's particularities and size must be considered, so that further studies will be able to consolidate these findings.

Also, the study brings to light the CP and VP, important markers of cardiovascular integrity level to be addressed in rehabilitation programs.[9] In addition, we also reinforce the need for studies to determine indicative cutoff values for patients diagnosed with T2DM.

Conclusion

In conclusion, CP and VP were similar in individuals with T2DM regardless of glycemic control. The predictive ability of these variables in health outcomes deserves to be further investigated in T2DM.

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Declarations

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Author contributions

Conceptualization, R.G.M., C.D.S. and L.M.S.; Methodology, R.G.M., C.D.S., L.M.S., L.B.L., C.I.M. and P.A.R.; Formal Analysis, L.M.S. and C.D.S.; Investigation, L.M.S., C.D.S., L.B.L., C.I.M. and P.A.R.; Resources, R.G.M. and A.B.S.; Data Curation, L.M.S. and C.D.S.; Writing – Original Draft Preparation, L.M.S.; Writing – Review & Editing, R.G.M., C.D.S. and L.B.L.; Supervision, R.G.M.; Project Administration, R.G.M.; Funding Acquisition, R.G.M. and A.B.S.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data that support the findings of this study are available on request from the corresponding author, RGM. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Ethics approval

The study was approved by the Human Research Ethics Committee of University (process number 2.814.754) and all individuals read and signed the free and informed consent form.

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