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ORIGINAL PAPER

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Arterial stiffness can predict cardiorespiratory fitness in type 2 diabetic patients?

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ABSTRACT

Introduction and aim. Arterial stiffness (AS) has been associated with reduced cardiorespiratory fitness (CRF). The aim of this study was to verify if there is a relationship between augmentations index (AIx), as an index for AS assessment, and CRF in individuals with type 2 Diabetes Mellitus (T2DM).

Material and methods. Observational cross-sectional study including 32 individuals diagnosed with T2DM who performed two evaluations: 1. Arterial stiffness assessment using SphygmoCor and 2. CRF throughout a cardiopulmonary exercise test on a treadmill ergometer. Oxycon Mobile® device was used to obtain oxygen uptake consumption at peak ($\dot{V}O_{2peak}$); oxygen uptake efficiency slope (OUES) determined by linear regression in reason of the logarithmic transformation of the ventilation and $\dot{V}O_2$ obtained every minute of exercise test. Statistical analysis comprised Pearson's Correlation and linear regression analysis performed in SigmaPlot.

Results. There was a significant correlation between AS and CRF: AIx and OUES; AIx@75 and; OUES. In linear regression, AIx was determinant for $\dot{V}O_{2peak}$ and OUES – AIx and; AIx@75 and $\dot{V}O_{2peak}$.

Conclusion. AS was associated with CRF in individuals with T2DM. These results contribute to the body of evidence linking arterial functional properties to CRF and suggests greater attention for this important index.

Keywords. augmentation index, cardiorespiratory fitness, type 2 diabetes

Introduction

Arterial stiffness (AS) has been widely recognized as a clinically relevant and independent prognostic cardiovascular biomarker.[1] Comorbidities such as hypertension, obesity and diabetes negatively impacts AS, as they accelerate the inflammatory process, increasing the vascular damage.[2] Hemodynamically, AS leads to an increased pulse wave velocity (PWV) and an early- reflected pressure wave to the heart.[3] As a consequence there is an overloaded systolic peak pressure and a decreased myocardial perfusion pressure.[3]

An alternative measure of the load inflicted on the central arterial and ventricular walls[2] is the augmentation index (AIx), an indirect measure that translates how much the central pulse pressure is responsible for the reflected pulse wave.[3] It is an index influenced by the diameter and elasticity of small arteries and arterioles.[3]

Individuals diagnosed with type 2 diabetes mellitus (T2DM) have a high prevalence rate of cardiovascular disease. Evidence of accelerated increase in AS and significant changes in central hemodynamics, cardiac function and structure have been observed in T2DM.[4]

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Advanced glycation end products in the elastic artery walls have been attributed as a causal factor of vascular dysfunction and increased AS.[4]

Wilkerson et al. respectivelyhave also demonstrated vascular function and skeletal muscle compromised in T2DM with vasodilation and increased blood flow impaired and reduced capillary density and dysfunctional capillary hemodynamics.[5]respectively Additionally, Baldi et al. have found T2DM associated with a reduced cardiorespiratory fitness (CRF) and lower peak oxygen uptake ($\dot{V}O_{2peak}$).[6] In this sense, vascular system is a component of the body´s ability to deliver oxygen to skeletal muscles during physical exercise contributing to CRF.

In addition to $\dot{V}O_{2peak}$, oxygen uptake efficiency slope (OUES) has been investigated as a function of the cardiopulmonary reserve that indicates the efficiency with which oxygen is extracted and taken to the body, with the advantage of not being affected by the intensity of the exercise.[7] Gajanand et al. showed that OUES can offer a valid submaximal measure for CRF for individuals diagnosed with T2DM integrating cardiovascular, musculoskeletal and respiratory functions.[8]

More specifically, association between increased AS and decreased CRF was previously verified in young, elderly and obese population.[3,9] Integrated responses are activated in physiologic systems to provide or improve the ability to sustain the physical exercise.[10] Cardiovascular response by maximal cardiac output directly correlates with CRF and $\dot{V}O_{2peak}$ and better CRF reflected in a lower systolic load and lower AIx.[3] Higher CRF and its beneficial anti-inflammatory also favorably affects vascular structure and function.[3]

Aim

Therefore, there seems to be a bidirectional association between AS and CRF, which has not yet been explored for the diabetic population. This study aimed to assess the relationship between AS and CRF in individuals diagnosed with T2DM. The hypothesis of the study is a presence of a negative association between AS and CRF in individuals with T2DM.

Material and methods

Study design and participants

A cross-sectional, observational, descriptive study was conducted from November 2018 to March 2019 in a sample of 32 individuals diagnosed with T2DM based on plasma glucose criteria according to American Diabetes Association, aged between 35 to 75 years old of both genders and who were invited through print and digital media and contact the researchers to voluntarily to participate in the study.[11] The non-inclusion criteria were individuals with a history of clinically proven cardiopathy and/or through examinations, vascular surgery of the carotid, femoral or aortic arteries, uncontrolled hypertension, cognitive disorders that interfere with the understanding of the experimental procedure, pregnant women and users of non-licit drugs. The exclusion criteria were factors potentially detrimental to the quality of the measurements or to make wave recording unreliable with low signal pickup, individuals who do not complete all assessments. This study was in accordance with the principles expressed in the Helsinki Declaration. 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. The individuals were instructed to avoid alcoholic drinks, coffee or any other stimulating drink the night before and the day of data collection; do not perform activities that required moderate to heavy physical effort the day before data collection and do not speak unnecessarily during the assessment to avoid interference during signal acquisition.

Study protocol

General evaluation

Personal data, clinical history and physical examination were assessed in all patients. Individuals were also asked about medications, family and previous history and physical activity level. The level of physical activity was considered according to the ACSM: practice less than 30 minutes of moderate activity five days a week or intense physical activity for 20 minutes on three days a week were considered sedentary.[12] Dyslipidemia and hypertension were attested by previous clinical diagnosis and Brazilian guidelines.[13,14] Body mass index (BMI) >30 kg/m^2 was considered as obesity.[15]

Arterial stiffness assessment

Pulse waves were obtained transcutaneously by SphygmoCor® device (AtCor Medical Pty Ltd, Australia) with transducers in the topography of the right carotid and right femoral arteries. Measurements were taken after a 10-minute of rest in the supine position. To determine the carotid-femoral pulse wave velocity, two pressure-sensitive transducers were placed on the skin, more specifically on prominent parts of the right common carotid and right femoral artery. The software used identifies R wave of the ECG and the base of the pulse wave to calculate the time and the speed in m/s that the wave takes to go through this stretch, which is, the distance traveled by the waves between the right carotid artery and the right femoral. Two measurements were performed with no difference greater than 5% between them and the mean of the two measurements was considered the cfPWV.[1]

Pulse wave analysis was also performed by the same device and were obtained systolic and diastolic central blood pressure (SBP and DBP, respectively) and central pulse pressure (PP) to obtain augmentation index

(AIx). AIx is defined as the difference between the second and the first peak of systolic pressure, denominated augmentation pressure (AP), expressed as a percentage of the pulse pressure (PP: the difference between systolic and diastolic pressure) (AIx% = [AP/PP] × 100). This index measures the increase in the AP during systole due to the reflex of the pressure waves that travel forward of the peripheral circulation. The AP can be considered an indirect measure of arterial elasticity, being obtained by the difference between the second systolic peak (referring to the reflected wave) and the first peak (wave resulting from ventricular systole). To avoid interindividual variability secondary to heart rate, AIx could be corrected for a heart rate of 75 beats per minute (AIx@75).[16]

Cardiopulmonary exercise test (CPET)

CPET was performed on a separate day and in the afternoon, avoiding any influence of the circadian rhythm. The test was performed in a treadmill ergometer (Super ATL, Porto Alegre, Rio Grande do Sul, Brasil) with incremental protocol in steps of Bruce and in the presence of a cardiologist.[17]using an open circuit technique, during the last 2 to 4 minutes of a multistage treadmill test of maximal exercise in 151 men and 144 women of 29 to 73 years of age. $\dot{V}o_{2max}$ was higher in men than in women (P < 0.0001 Ventilatory and metabolic variables were recorded using a portable system Oxycon Mobile® (Mijnhardt/Jäger, Würzburg, Alemanha). Individuals were encouraged to perform the test until exhaustion and the criteria for test interruption were as described by Baladi.[18] $\dot{V}O_{2peak}$ was identified as the highest value observed during the final 30 seconds of the test.[18] Oxygen uptake efficiency slope (OUES) was determined by linear regression in reason of the logarithmic transformation of the ventilation (VE) and oxygen consumption ($\dot{V}O_2$) obtained every minute of CPET using the following equation ($\dot{V}O_2$ = a log VE + b), providing an accurate mathematical model for the analysis of respiratory gas exchange during incremental exercise.[7] In this equation, the constant 'a' represents the OUES coefficient and 'b' represents the intercept. Glucose levels were monitored before and after CPET and to values lower than 100 mg/dl, 15 g to 30 g of carbohydrate was offered before exercise. When blood glucose was greater than 250 mg/dl, the test was rescheduled.[19]

Statistical analysis

A posteriori power analysis was performed using GPower® *3.1 (Kiel University, Germany). Considering our sample size of* 32 individuals and a 5% error, statistical power was calculated to be 80% with and effect size of 0.46. The descriptive data were presented as mean and standard deviation. The Shapiro-Wilk test verified the data distribution. Pearson's Correlation were used to investigate relationship between AS measurements (AIx, AIx@75, and PWV) and $\dot{V}O_{2peak}$ and between AS measurements and OUES. Univariate and multiple regression analysis (adjusted for age and BMI) were also performed to identify vascular determinants for CRF ($\dot{V}O_{2peak}$ and OUES). A logarithmic transformation for the BMI was applied in order to fulfill the assumption of normality. Intraclass Correlation Coefficient was applied according Hopkins (2000) classification: 0 to 0.3 was considered a small correlation, 0.31 to 0.49 moderate, 0.50 to 0.69 large, 0.70 to 0.89 very large and 0.90 to 1.00 near perfect.[19] All tests were made in SigmaPlot 11.0 (Systat Software Inc., USA) and significant values were considered when p<0.05.

Table 1. Clinical, anthropometric, comorbidity characteristics and medications in T2DM individuals[a]

General Features	**N = 32**
Age, years	54.25 (9.07)
Men, n (%)	22 (66)
Weight, kg	85.55 (18.02)
Height, m	1.72 (0.11)
BMI, kg/m²	29.00 (5.07)
Diagnosis, months	83.97 (70.71)
Menopause, n (%)	7 (21.9)
Hb1Ac, %	8.03 (1.76)
Risk Factors	
Obesity, n (%)	13 (40.6)
Smoker, n (%)	3 (9.4)
Sedentary, n (%)	20 (62.5)
Hypertension, n (%)	14 (42.7)
Dyslipidemia, n (%)	18 (56.2)
Medications	
SGLT 2 Inhibitors, n (%)	7 (21.9)
Sulfonylurea, n (%)	10 (31.2)
Biguanide, n (%)	23 (71.9)
Glyptin, n (%)	4 (12.5)
Insulin, n (%)	8 (25.0)
Diuretic, n (%)	5 (15.6)
Angiotensin-Converting Enzyme Inhibitors, n (%)	1 (3.1)
Angiotensin II Receptor Blockers, n (%)	8 (25.0)
Beta-Blockers, n (%)	3 (9.4)
Lipid reducer, n (%)	8 (25.0)

[a] The data presented are described as mean (standard deviation) and in percentage of individuals in the sample. BMI: body mass index; SGLT-2: sodium/glucose cotransporter 2

Results

A total of fifty-two individuals were initially recruited, however, seventeen were excluded for not having completed the tests, one was excluded for presenting outliers and 2 were excluded for having a diagnosis of prediabetes. Therefore, thirty-two individuals were included in

the final sample of this study. The Table 1 shows sample characterization regarding general features, risk factors and medications. More than half of our population was classified as sedentary, diagnosed with dyslipidemia and has no controlled glycemia, as indicated by an analysis of glycated hemoglobin (Hb1Ac).

Table 2. Variables of arterial stiffness and peak CPET[a]

Arterial stiffness and hemodynamics measurements	
ASP, mmHg	123.28 (16.11)
ADP, mmHg	83.22 (8.75)
PP, mmHg	39.56 (11.68)
MAP, mmHg	99.19 (11.6)
HR, bpm	71.09 (10.45)
AP, mmHg	10.44 (5.7)
AIx, %	25.25 (8.79)
AIx@75, %	23.81 (7.53)
BSP, mmHg	135.50 (18.99)
BDP, mmHg	82.31 (8.62)
PPA, mmHg	12.22 (4.88)
PWV, m/s	8.33 (1.53)
PTT, ms	48.56 (8.49)
Cardiorespiratory exercise test variables (peak)	
HR, bpm	156.19 (20.2)
% HR_{max}	92.95 (19.6)
$\dot{V}O_2$, mL/kg^{-1}.min^{-1}	22.40 (3.56)
Systolic BP, mmHg	200.71 (30.74)
Diastolic BP, mmHg	101.19 (13.42)
VE/VCO_2 slope	40.54 (7.66)
OUES	2.00 (0.5)
RER	1.15 (0.12)
O_2P, mL/beat	12.61 (2.91)

[a] The data presented are described as mean (standard deviation). ASP: Aortic Systolic Pressure; ADP: Aortic Diastolic Pressure; PP: Pulse Pressure; MAP: Medium Arterial Pressure; HR: Heart Rate; AP: Augmentation Aortic Pressure; AIx: Augmentation index; AIx@75: Augmentation Index at the heart rate of 75 beats min^{-1}; BSP: Brachial Systolic Pressure; BDP: Brachial Diastolic Pressure; PPA: pulse pressure amplification; PWV: Pulse Wave Velocity; PTT: Pulse Transit Time; $\dot{V}O_{2peak}$: Oxygen Uptake; VE/VCO_2 slope: linear relation between minute ventilation and carbon dioxide production; OUES: oxygen uptake efficiency slope; RER: respiratory exchange ratio; % HRmax: maximum heart rate reached in percentage; O_2P: oxygen pulse

The results of the AS and CPET are outlined in Table 2 and it is possible to note that the individuals are considered with poor CRF.[21] According to the Brazilian Society of Hypertension, 6 individuals were considered to be at stage 1, 2 and 3 of hypertension (1, 2 and 1, respectively). Regarding the amplification of pulse pressure, characterized by the difference in brachial systolic pressure and aortic systolic pressure, individuals are within the normal range.[22,23]

The Figure 1 shows the correlation between AS with $\dot{V}O_{2peak}$ and OUES. Considering significant correlations found between CRF and AS measurements, a simple linear regression analysis was performed (Table 3) and a small correlation was identified. There was a significant correlation between both AS variables with OUES; however, predicting results of analysis to OUES with Aix was better than Aix75. In the OUES estimation model based on the AIx, it was able to explain 28% of OUES variance, and the following predictive equation was obtained: OUES = 2.76 – (0.03 × AIx). The regression coefficient associated with AIx was 0.03 suggesting that each one-unit increase in AIx is associated a 0.03 unit decrease in OUES.

To $\dot{V}O_{2peak}$ estimation model based on the AIx@75, this variable was able to explain 23% of $\dot{V}O_{2peak}$ variance, and the following predictive equation was obtained: $\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1}) = 27.82 – (0.23 × AIx@75). The regression coefficient associated with AIx@75 was 0.23 suggesting that each one-unit increase in AIx@75 is associated a 0.23 unit decrease in $\dot{V}O_{2peak}$.

Discussion

The aim of this study was to evaluate the association between AS and CRF, namely $\dot{V}O_{2peak}$ and OUES in individuals diagnosed with T2DM. The main findings of the study were: I) there was an association between arterial stiffness (AIx and AIx @ 75) and CRF ($\dot{V}O_{2peak}$ and OUES); II) AIx was determinant for $\dot{V}O_{2peak}$ and OUES.

As mentioned before, AIx is an indirect measurement of AS that represents the difference between the first and the second systolic peaks expressed as a percentage of pulse pressure and it is explained by the reflected pulse wave.[2,16,24] In this way, although PWV has been considered as the standard measure for AS, AIx is a substitute measure for the load inflicted on central arterial and ventricular walls.[2]

In addition, AIx is also important as an independent marker of premature coronary artery disease, a strong independent predictor of congestive heart failure and all-cause mortality in healthy and clinical populations.[24] In an apparently healthy population, Janner et al. found an average value of AIx: 21.8 for men and 30.0 for women.[24] In addition, Solanki et al. observed the following results for apparently healthy individuals from 35 to 44 years old AIx@75 results – 30.03 (9.88), from 45 to 54 years old - 29.38 (11.37), 55 to 65 years old - 32.10 (11.85).[24] Our findings regarding AIx corroborate these values found in the literature. Given the importance that AIx has gained in the literature, it deserves to be more investigated.

In people with T2DM, the study by Brooks et al. reveals an direct effect of the disease in AIx.[4] The author explains that this influence may be due to changes in the stiffness of the artery wall due to glycation, calcification

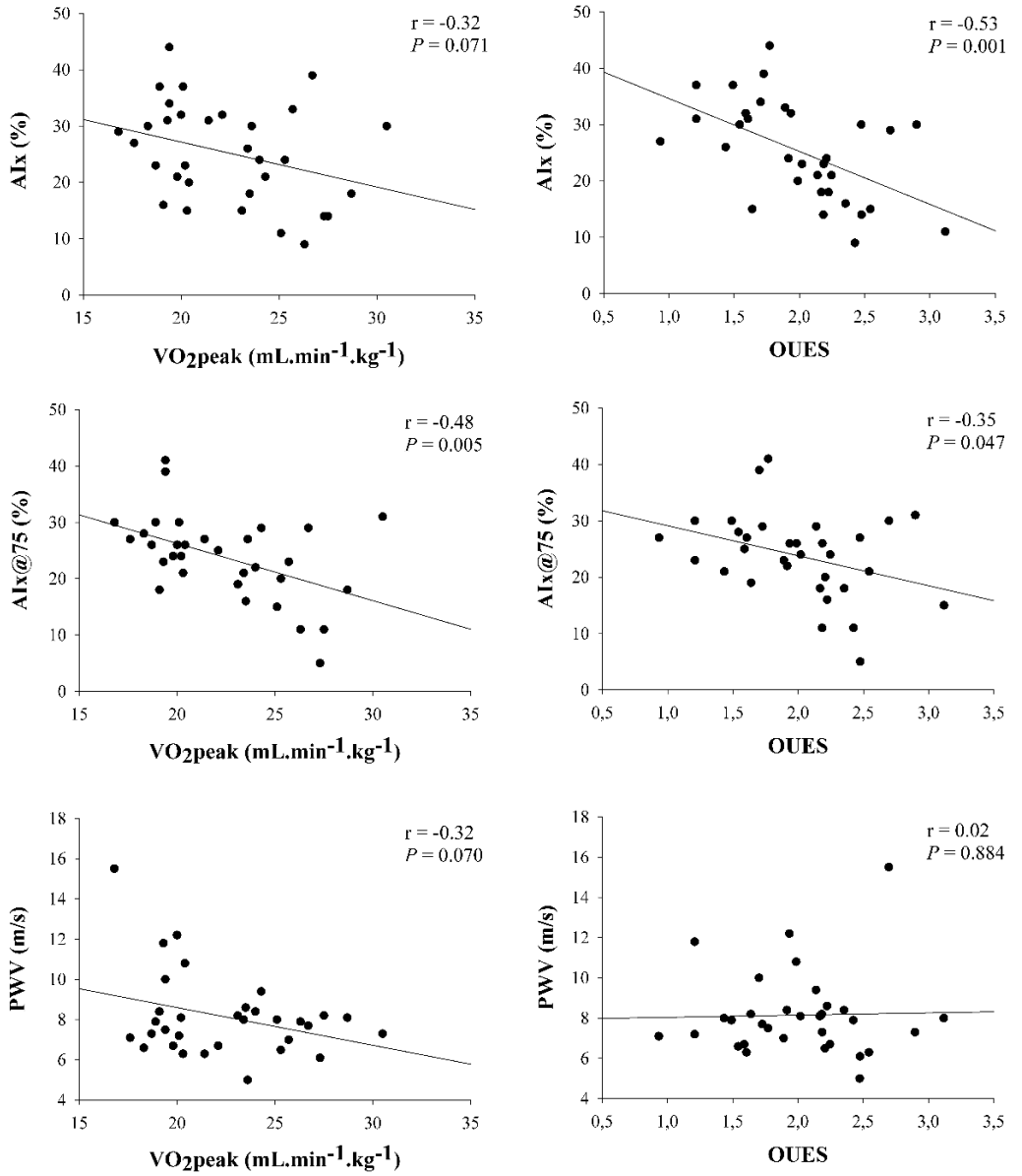

Fig. 1. Correlations between arterial stiffness measurements and oxygen uptake ($\dot{V}O_{2\,peak}$) on the right and between arterial stiffness measurements and oxygen uptake efficiency slope (OUES) on the left. AIx: augmentation index; AIx@75: augmentation index standardized to a heart rate of 75 beats per minute; PWV: pulse wave velocity

and changes in the composition of the extracellular matrix. In addition to negatively influencing vascular measurement, diabetes is also an independent predictor of cardiovascular disease and is associated with low CRF, which is another cardiovascular risk factor.[6]

The relationship of AIx with cardiorespiratory variables in individuals with T2DM is still poorly studied, however some studies showed the influence of AIx on $\dot{V}O_{2peak}$ in other populations.[3,16] Binder et al. evaluated asymptomatic men and obtained as a result that AIx is significant and inversely related to $\dot{V}O_{2peak}$ before and after confounding adjustments such as age, heart rate, body mass index and others. Denham et al. compared endurance and control athletes and concluded that there is a difference in the AIx values between the groups, but this difference is attenuated when the values were normalized by the $\dot{V}O_{2peak}$ value.[16] In addition, they concluded that moderate levels of CRF help achieve lower AIx values, avoiding adverse loading on the heart and large arteries and mitigating the risk of future cardiovascular events and all-cause mortality.

Denham et al. explains that the improvement in $\dot{V}O_{2peak}$ reflects cardiovascular adaptations associated with physical exercise.[16] Exercise increases circulating endothelial progenitor cells known to maintain the integrity of the internal arterial wall. High laminar shear stress,

subsequent release of endothelial nitric oxide by nitric oxide synthase and increased circulating EPC caused by repeated and prolonged resistance exercise sessions, influence lower blood pressure and AIx in athletes. Corroborating these data, another study explains that CRF has an anti-inflammatory and antithrombotic effect, which may affect the vascular structure and function.[3] These studies help to explain the relationship found between the variables of AS and CRF.

Table 3. Univariate regression: $\dot{V}O_2$peak estimation model based on AIx@75 (Model 1) and OUES estimation model based on AIx (Model 2)[a]

Variable	Coefficient	Standard error	P Value
Model 1 – $\dot{V}O_2$peak			
R^2 0.231			
Constant	27.82	1.89	<0.001
AIx@75 (%)	-0.23	0.076	0.00
Model 2 – OUES			
R^2 0.284			
Constant	2.76	0.23	<0.001
AIx (%)	-0.03	0.01	0.00

[a] $\dot{V}O_2$: oxygen uptake; AIx@75: augmentation index standardized to a heart rate of 75 beats per minute; OUES: oxygen uptake efficiency slope; AIx: augmentation index

Table 4. Multivariate regression: $\dot{V}O_2$peak estimation model based on AIx@75 (Model 1) and OUES estimation model based on AIx (Model 2)[a]

Variable	Coefficient	Standard error	P value
Model 1 – $\dot{V}O_{2peak}$			
Age (years)	-0.10	0.06	0.12
BMI* (kg/m^2)	-12.96	7.82	0.11
AIx@75 (%)	**-0.17**	**0.08**	0.04
Model 2 – OUES			
Age (years)	-0.01	0.01	0.29
BMI* (kg/m^2)	3.21	0.89	0.00
AIx (%)	**-0.02**	**0.01**	0.00

[a] $\dot{V}O_2$: oxygen uptake; AIx@75: augmentation index standardized to a heart rate of 75 beats per minute; OUES: oxygen uptake efficiency slope; AIx: augmentation index, *Natural logarithm transformed variables, Model 1: R^2 = 0.336; Adjusted R^2 = 0.265; P = 0.009; Model 2: R^2 = 0.536; Adjusted R^2 = 0.486; P < 0.001.

Despite our findings regarding AIx corroborating the literature, the results related to PWV are still contradictory. Augustine et al. obtained an inversely significant result between PWV and $\dot{V}O_{2máx}$ in obese middle-aged women.[9] On the other hand, some studies have also found no significant relationship between the cardiorespiratory and AS variables.[27,28]

Some studies show that AIx and PWV are influenced by different anatomical and physiological properties[24], what can explain this difference found in our study. The increased reflection and stiffness of the arterial waves cause an increase in the systolic load in the heart, limit the cardiac output during exercise and, thus, can reduce $\dot{V}O_2$.[3] In addition, Wilkinson et al. shows that the PWV is not affected by changes in heart rate, while AIx is influenced by this variable.[27] This explanation helps to reinforce our findings and the importance of adjusting AIx by heart rate. Our findings show that only AIx@75 was determinant for $\dot{V}O_{2peak}$ and it can be explained by the relationship between heart rate and AIx that occurs due to the reduction in ejection duration, causing a change in the wave reflected in the diastole.[4]

Another possible explanation is that some studies indicate that PWV increases with age, while AIx tends to stabilize after 60 years old.[24] This plateau can be explained by the reduction of impedance incompatibility between the peripheral and central arteries, decreasing the amplitude of the reflection and altering the location of the reflection of the pulse wave distally.[24] However, although the population studied was diagnosed with diabetes, the PWV was not yet characteristic of AS, that is, above 10 m/s as established by Van Bortel et al.[1] In addition, the association of AS and CRF is stronger in individuals with more advanced clinical cases and the average diagnosis time for our population is 6 years.[28]

Regarding OUES, it is known that it is a variable that reflects the integration of function and health of the skeletal, cardiovascular and pulmonary muscular systems and indicates the effectiveness with which oxygen is absorbed and distributed to the body.[7]"container-title":"Journal of the American College of Cardiology"",""-DOI":"10.1016/S0735-1097(96[10] A possible explanation for the association between AIx and OUES found in our study is metabolic acidosis, which acts on the inflammatory process of the arterial wall, releasing cytokines that can induce vascular calcification. The development of metabolic acidosis is one of the physiological bases of OUES, as it controls the distribution of blood to skeletal muscles.[7]"container-title":"Journal of the American College of Cardiology"",""DOI":"10.1016/S0735-1097(96

Although the study subjects have an OUES value within the expected, according to Myers et al., the minute ventilation/carbon-dioxide output value is slightly above the established, showing a poor prognosis and a moderate risk of cardiovascular events.[31] On the other hand, our findings regarding this variable corroborate the findings of Gürdal et al., because it is known that exercise capacity is impaired in the population diagnosed with T2DM.[32]

Conclusion

The AIx could be considered a predictive variable of CRF, since our results showed an association between AIx with OUES and AIx@75 with $\dot{V}O_{2peak}$ in individuals diagnosed with T2DM. Despite the small sample, which

is a possible limitation of our study, these findings are clinically important, AIx is easily accessible and non-invasive and has been shown to be an important measure of AS. As an important predictor of cardiovascular impairment and with proved cardiorespiratory performance association, greater attention is suggested for this important vascular variable. These results contribute to the body of evidence linking arterial functional properties to cardiorespiratory fitness.

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Declarations

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Author contributions

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

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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