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CARDIOPULMONARY TESTING IN THE DIAGNOSIS OF CORONARY HEART DISEASE: THE ACCURACY OF THE OXYGEN PULSE CURVE

TESTE CARDIOPULMONAR NO DIAGNÓSTICO DE DOENÇA CORONARIANA: ACURÁCIA DA CURVA DO PULSO DE OXIGÊNIO

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ABSTRACT

Exercise-induced myocardial ischemia, at significant levels, may interfere in the increase of systolic volume and cause deflection of the PuO_2 curve. A change of the curvilinear response of PuO_2, which results in a flattening of the curve, demonstrates a reduction of the systolic volume and/or failure to increase the extraction of oxygen. In a non-systematic literature review, we found few publications about the deflection of the PuO_2 curve, secondary to exercise-induced ischemia, totaling only nine studies over 22 years, and including 339 patients. The sensitivity and the specificity of the ET were 46% and 66%, respectively; the sensitivity and the sensibility of the CPT reached 51% and 60%, respectively, considering the deflection of PuO_2. When the deflection of PuO_2 was associated with the relationship between VO_2/work rate slope, the sensibility and specificity reached 87% and 74%, respectively. In the subgroup with extensive ischemia, peak PuO_2 was reduced as compared to the subgroup with mild ischemia (12.8±3.8 vs. 16.4±4.6 - $p < 0.05$), showing that there may be a flattening of the curve in cases with extensive myocardial ischemia. There was an increase in PuO_2 from 11.76 to 13.27 ml/beat and of the slope of PuO_2 from 7.05 to 9.25 following coronary angioplasty. There are indications that the use of cardiopulmonary testing may be useful in the diagnosis of coronary heart disease, detecting more serious cases.

Keywords: Oxygen Pulse; Cardiopulmonary Testing; Coronary Heart Disease.

RESUMO

A isquemia miocárdica induzida por esforço em níveis significativos interferiria no aumento no volume sistólico e levaria à deflexão da curva do PuO_2. A alteração da resposta curvilínea do PuO2, que resulta em achatamento da curva, demonstraria redução do volume sistólico e/ou falha para aumentar a extração de oxigênio. Em revisão não sistemática da literatura, encontramos poucos relatos sobre a deflexão da curva do PuO_2 secundária à isquemia induzida por esforço, totalizando apenas nove estudos em 22 anos, que abrangeram 339 pacientes. A sensibilidade e a especificidade do TE foi de, respectivamente, 46% e 66%; a sensibilidade e a especificidade do TCP atingiram, respectivamente, 51% e 60%, considerando-se a deflexão do PuO_2. Quando a deflexão do PuO_2 foi associada à relação entre VO_2/work rate slope, a sensibilidade e a especificidade atingiram 87% e 74%, respectivamente. No subgrupo com isquemia extensa, o pico do PuO_2 foi reduzido em comparação com o subgrupo com isquemia discreta (12,8 ± 3,8 vs. 16,4 ± 4,6 – $p < 0,05$), demonstrando que a deflexão da curva de PuO_2 pode estar presente nos casos de isquemia miocárdica extensa. Houve elevação do PuO_2 de 11,76 para 13,27 ml/batimento e do slope de PuO_2 de 7,05 para 9,25 depois de angioplastia coronariana. Há indícios de que a utilização do teste cardiopulmonar no diagnóstico da doença coronariana pode ser útil, rastreando os casos de maior gravidade.

Descritores: *Pulso de Oxigênio; Teste Cardiopulmonar; Doença Coronária.*

INTRODUCTION

Currently, there are studies that seek to demonstrate the usefulness of the Cardiopulmonary Test (CPT) in the diagnosis of Atherosclerotic Coronary Disease (ACD).

In 2002, the American College Cardiology and the American Heart Association published an extensive meta-analysis involving 147 studies covering 24047 patients, giving the exercise stress test 68% sensitivity, 77% specificity and

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73% accuracy for DAC diagnosis. According to bias, these values ranged from 50 to 72%, 69 to 90% and 68 to 75% respectively. In general, the accuracy of ET was higher in cases without ST changes or left ventricular overload on the resting control ECG, respectively, 75% versus 69%, and 74% versus 68%.[1]

This data has stimulated further studies to improve the performance of ET in diagnosing ACD. One of the proposals was the use of gas exchange analysis during ET, that is, TCP, to measure the Oxygen Pulse (PuO_2) response during incremental exercise. (Table 1)

Currently, the specialized literature still brings a small number of articles about it, stimulating the dissemination of existing studies.

Table 1. Fick principle and estimate of Systolic Volume.[2]

Fick Principle: VO_2 = Cardiac Output x C (a-v)O_2
Cardiac Output = FC x Systolic Volume
VO_2 = FC x Systolic Volume x C (a-v)$_{O2}$
VO_2 / FC = Systolic Volume x C (a-v)O_2
PuO_2 = VO_2 / FC
PuO2 ≈ Systolic Volume
Example: VO_2 = 1.20 L/min STPD, FC = 120 beats
PuO_2 = 1.2 x 1000 / 120 = 10 ml STPD/beat
Stroke Volume ≈ 10 ml/beat

VO_2 = Oxygen Consumption; FC = Heart Rate; C (a-v)O_2 = Arteriovenous Difference of O_2; PuO_2 = Oxygen Pulse; STPD: Standard Temperature Pressure, Dry (Temperature = 0°C; Atmospheric Pressure = 760 mmHg (dry).

PHYSIOLOGICAL BASES

PuO_2 is calculated by dividing oxygen consumption (VO_2) by heart rate (HR) and expressed in ml/beat, allowing the estimation of systolic volume. The normal VO_2/HR ratio is curvilinear, hyperbolic, with rapid elevation at low workloads and followed by slow elevation, representing asymptotic values, that is, the rate of increment decreases gradually as the maximum values approach.[3]

According to the American Thoracic Society/American College of Chest Physicians, PuO_2 peak values can be estimated by the formula where height is given in cm, and values for 0 (male) and 1 (female) are used for gender.[4]

$$PuO_{2\,PEAK} = 0.28\,(Height) - 3.3\,(Gender) - 26.7 \pm 2.8$$

PuO_{2PEAK} varies according to body surface, age, gender, physical fitness and hemoglobin concentration, reaching up to 5 ml/beat (7-year-old child), or even to 17ml/beat (30-year-old man, 1.9 m height)[5] Reference values for bicycle testing are shown in Table 2. Levels above 80% of the predicted values are recommended.[3] Values above the predicted for age/gender are found in individuals with good physical condition and in patients in use of beta-blocker.[5]

During incremental exercise, increases in cardiac output are accompanied by increases in systolic volume and heart rate; In moderate to intense exercise, the increases in cardiac output are due to increases in heart rate.[3]

PuO_2 increases with incremental exercise due to increases in systolic volume and peripheral oxygen extraction, as measured by the arteriovenous O_2 difference [C (a-v) O_2]. The maximum values of peripheral O_2 extraction reach 75% of arterial O_2 content in apparently healthy non-athletes. At peak exercise, C(a-v) O_2 remains constant and it is assumed that changes in PuO_2 reflect changes in stroke volume.[3]

Table 2. Reference values for maximal exercise stress testing in bicycle, including oxygen pulse, according to ATS/ACCP[2, 4, 24, 25]

Variables	Equations
VO_2 (ml/min) – man	P x (50,75 - 0, 372 I)
VO_2 (ml/min) – woman	(P + 43) x (22.78 - 0.17 I)
FC ((beat/min)	210 - 0.65 I
PuO_2 (ml/(beat)	$VO_{2predicted\ peak}$ /$FC_{predicted\ peak}$
Anaerobic Threshold	40% $VO_{2predicted\ peak}$

I = Age in years; P = Weight in kg; A = Height in cm. Predicted Weight = 0.79 x A – 60.7 (man); Predicted Weight = 0.65 x A – 42.8 (woman).

Plateau PuO_2 curve, showing unchanged values with increasing workload, can be interpreted as a reduction in stroke volume and or insufficient values of oxygen extraction by skeletal muscles. These findings may reflect physical deconditioning, cardiovascular disease, or limitations that occur in early exercise motivated by symptoms or ventilatory disorders.[3]

OXYGEN PULSE AND MYOCARDIC ISCHEMIA CURVE

Echocardiography has shown that reversible regional myocardial ischemia alters regional contractility and systolic thickening, which can be abolished; after recovery, these variables return to normal. The reduction in regional systolic thickening occurs as early as the reduction in contraction dP/dt before ST segment changes.[8]

Stress-induced ischemia, at significant levels, would interfere with the increase in systolic volume and cause the inflection of the PuO_2 curve during incremental exercise. Inbar et al. reported elevations of VO_{2PEAK} from 17.49 to 20.75 ml/kg/min, anaerobic threshold from 12.15 to 14.39 ml/kg/min, PuO_2 from 11.76 to 13.27 ml/beat and the PuO_2 slope from 7.05 to 9.25 after coronary angioplasty.[9] Castro et al. found in patients with ACD that pyridostigmine, an anticholinesterase agent, significantly increased $VO_{2\,PEAK}$ and $PuO_{2\,PEAK}$ compared to placebo (24.8 vs. 23.6 ml/kg/min and 13.6 vs. 12.9 ml/beat).

In a non-systematic review of the specialized literature, we found few reports about the deflection of the PuO_2 curve secondary to induced exertion ischemia, totaling only 310 patients studied and published over 10 years.[11-17]

In 2002, Klainman et al. studied 46 patients with ACD using TCP and (99m)Tc radioisotopic ventriculography. PuO_2 response curves were classified into four categories: 1) Type A, normal curve, with curvilinear aspect, to which they assigned a 10-point score; 2) Type B, curvilinear aspect curve, with reduced PuO_2 values, to which they attributed an eight-point score; 3) Type C, curve with reduced PuO_2 values, inflection, ending in plateau, to which they assigned a five-point score; 4) Type D, PuO_2 downward curve, to which they attributed a two-point score. They reported a high correlation ($p < 0.001$; $R = -0.89$) between the PuO_2 score and the presence of ischemia and ventricular dysfunction, concluding that PuO_2 response curve was a useful noninvasive procedure capable of discriminating patients with ACD and ventricular dysfunction. However, PuO_2 curve score did not allow to detect cut-off value for clinical application.[11]

In 2003, Belardinelli et al. in a pioneer researching, studied 202 patients with proven ACD, 173 men, 55.7 ± 10.8 years,

who underwent CPB and myocardial perfusion scintigraphy, which was considered the gold standard. In this report, ET sensitivity and specificity were 46% and 66%, respectively, considering ST segment analysis; TCP sensitivity and specificity reached 51% and 60%, respectively, considering PuO_2 deflection. When PuO_2 deflection was associated with the relationship between VO_2/work rate slope, sensitivity and specificity reached, respectively, 87% and 74%.[12]

In 2007, Munhoz et al. found no significant changes in PuO_2 curves in 87 middle-aged patients, 56 men, referred for myocardial perfusion scintigraphy. During exercise, patients achieved similar PuO_2 values in the groups with and without ischemia, respectively: 25% peak VO_2 peak , 9.7 ± 2 vs. 9.3 ± 2 ml/beat; 50% VO_2 peak, 11.2 vs. 10.8 ± 3 ml/beat; 75% $V0^2$ of the peak, 12.5 ± 3 vs. 11.9 ± 3 ml/beat; VO^2peak, 13 ± 4 vs. 13.4 ml/beat (p = NS). However, in the subgroup with extensive ischemia (SSS, summed stress score> 13 and SDS, summed difference score> 7), PuO_2 peak was reduced compared to the subgroup with mild ischemia (12.8 ± 3.8 vs. 16. 4 ± 4.6 - p <0.05), demonstrating that PuO_2 curve deflection may be present only in cases with extensive myocardial ischemia.[13]

Typical examples of depressed PuO_2 curve have been published as case reports by some authors.[14-17]

Contini et al. described a case of a middle-aged man who reported a feeling of discrete precordial discomfort after intense physical activity. Exercise testing was normal and TCP revealed PuO_2 curve deflection. Upon finding a right coronary artery lesion, the patient underwent transcutaneous angioplasty with stent implantation, normalizing the PuO_2 curve in subsequent TCP.[14]

Chaudry et al. reported a case of a 68-year-old female smoker with hypertension and dyslipidemia. During TCP, from 93bpm, there was a reduction in PuO_2, maintaining the ECG without abnormalities. Coronary angiography showed occlusion> 95% of right coronary artery.[15]

Chaudhry et al. reported a case of a 36-year-old asymptomatic man with dyslipidemia, who had a depressed PuO_2 curve, which regressed to repeated TLC in three years after aggressive treatment of cholesterol levels.[16]

Chaudhry et al. reported a case of a 56-year-old female smoker with hypertension with chest discomfort and a depressed PuO_2 response. Cardiac exams - echocardiogram, myocardial perfusion scintigraphy and coronary angiography were normal. Abnormal PuO_2 response was abolished after ranolazine use, the case was diagnosed as suspected microvascular ischemia.[17]

However, Pakulin et al. performed TCP in patients with ACD and control group; The patients with ACD had $VO_{2\ PEAK}$, anaerobic threshold lower than controls, and similar PuO_2 values in both groups.[18]

PuO_2 response is related to systolic volume and peripheral O_2 extraction. Systolic Volume is linked to the behavior of the left ventricular ejection fraction (LVEF). Peripheral O_2 extraction, assessed by the arteriovenous O_2 [$C(a\text{-}v)O_2$] difference, would be able to compensate for minor reductions in systolic volume while maintaining aerobic balance.

Ponkan et al. studied the behavior of LVEF in incremental tests. In athletes, LVEF increased to the second lactate threshold, when it tended to constant values. In normal, non-athlete individuals, LVEF increased to the second lactate threshold, with a fall thereafter. In an incremental test, 59 ± 7 days after myocardial infarction, LVEF values were 47 ± 3% (rest), 50 ± 1% (Phase I, up to the first lactate threshold), 51 ± 2% (Phase II, until the second lactate threshold) and 45 ± 2% (Phase III, after the second lactate threshold).[19]

Foster et al. demonstrated that the left ventricular ejection fraction is reduced during incremental testing in patients with effort-induced ischemia. The ejection fraction values in groups 1 (DCA with ischemia), 2 (DCA without ischemia) and 3 (control) at rest and at peak exertion reached, respectively: 58% and 54% versus 43% and 51% versus 59% and 61%.[20]

Hsi et al. demonstrated that body weight-corrected PuO_2 correlated significantly with left ventricular ejection fraction assessed by radioisotopic ventriculography in post-myocardial infarction patients.[21]

PULSE OF OXYGEN AND GROWTH HORMONE DEFICIENCY

Growth Hormone Deficiency Syndrome (GHD) is characterized by lipid abnormalities (increased total cholesterol and LDL-cholesterol, hypertriglyceridemia and reduced HDL-cholesterol), insulin resistance, visceral obesity, reduced aerobic capacity and higher incidence, atherosclerosis, cardiovascular disorders, which play an important role in the prognosis.[22]

In patients with GHD, Conceição et al. observed a reduction in $VO_{2\ PEAK}$ and $PuO_{2\ PEAK}$ in respectively 92% and 69% of the cases. $VO_{2\ PEAK}$ reduction was 59.9 ± 9.9% compared to the predicted. $PuO_{2\ PEAK}$ values reached 8.4 ± 2.8 ml/beat. Correlations between PuO_2 and serum IGF-1 level (p = 0.002), and PuO_2 and body mass index (p = 0.007) were described.[23] Shahi et al. reported a correlation between IGF-1 and left ventricular mass (r = 045, p <0.02).[24] Beshiah et al. found that hormone replacement increased exercise tolerance; however, there were no changes in ventricular dimensions and left ventricular ejection fraction.[25]

CONCLUSION

Small area-restricted myocardial ischemia does not appear to change PuO_2 peak values; however, areas of extensive ischemia could interfere with systolic volume, reducing $PuO_{2\ PEAK}$, and constituting markers of poor prognosis.

Thus, the PuO_2 response in TCP, although useful in some cases, seems to add little value to the accuracy of TCP in detecting induced stress ischemia. Its usefulness would be restricted to cases with extensive areas of ischemia.

The existing literature is still insufficient, covering few reports and very few patients. Further studies will be needed to clarify the true value of the PuO_2 curve in the assessment of myocardial effort induced coronary artery ischemia, ultimately determining its sensitivity and specificity.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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