Value of the oxygen pulse curve for the diagnosis of coronary artery disease

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Short title: oxygen pulse curve and coronary artery disease

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Summary

This study investigated the value of oxygen (O2) pulse curves obtained during cardiopulmonary exercise testing (CPET) for the diagnosis of coronary artery disease (CAD). Forty patients with known coronary anatomy (35.0% normal, 27.0% single-vessel and 38.0% multivessel CAD) underwent CPET with radiotracer injection at peak exercise, followed by myocardial scintigraphy. O2 pulse curves were classified as: A-normal, B-probably normal (normal slope with low peak value); C- probably abnormal (flat, with low peak value); or D- definitely abnormal (descending slope). Sensitivity, specificity, positive and negative predictive values of the O2 pulse curve pattern (A or B vs C or D) for the diagnosis of CAD were, respectively, 38.5%, 81.3%, 76.9%, and 44.8%. The concordance rate between the abnormal O2 pulse curve pattern and ischemia in myocardial scintigraphy was 38.1%. Age and the extent of scintigraphic perfusion defect, but not the abnormal O2 pulse curve patterns (B or C or both combined) were independently associated with CAD. In conclusion, the O2 pulse curve pattern has low diagnostic performance for the diagnosis of obstructive CAD, and the abnormal curve pattern was not associated with myocardial ischemia defined by scintigraphy.

Keywords: cardiopulmonary exercise testing; oxygen pulse; myocardial perfusion scintigraphy; myocardial ischemia; coronary artery disease; diagnosis

Introduction

Cardiopulmonary exercise testing (CPET)- exercise testing with ventilatory gas exchange measurements- provides a wide array of clinically useful information. While frequently employed in the heart failure scenario to assess the degree of cardiac dysfunction and prognosis, CPET has a number of other indications, from the evaluation of athletic performance in healthy individuals to testing for the presence of coronary artery disease (CAD) (Myers & Gullestad, 1998; Balady et al, 2010; Guazzi et al, 2012). Beyond more "popular" variables such as VO2 max, the maximal oxygen consumption during exercise, other variables such as the oxygen pulse (O2 pulse) and its derived curve have emerged as potential indicators of cardiovascular disease.

The O2 pulse is the ratio of VO2 to heart rate and reflects the amount of O2 extracted per heart beat, providing an estimate of left ventricular stroke volume changes during exercise, if anemia is not present. The normal physiological response to progressive exercise is a continuously increasing O2 pulse, a linear increase in $\dot{V}O_2$ versus work rate, and a linear increase in heart rate versus $\dot{V}O_2$ until peak values are reached (Whipp et al, 1996; Klainman et al 2002; Lim et al, 2005). The development of myocardial ischemia during exercise can lead to loss of augmentation of stroke volume, which appears as a flattening of the O2 pulse curve. A flat or downward O2 curve has been suggested to indicate the presence of exercise-induced myocardial ischemia assessed by myocardial perfusion imaging (Belardinelli et al, 2003; Muñoz et al, 2007). We have recently shown, however, an association between myocardial fibrosis and O2 pulse abnormality (De Lorenzo et al, 2017). It remais to be demonstrated, though, the value of the O2 pulse curve pattern for the diagnosis of the presence and extent of CAD using invasive coronary angiography as the gold standard.

Thus, the aim of this study was to evaluate the diagnostic properties of the O2 pulse curve in patients with known coronary anatomy who underwent CPET with radiotracer injection for myocardial perfusion scintigraphy, a protocol which also allows for the evaluation of myocardial ischemia and fibrosis in addition to other physiological data obtained at CPET.

Methods

Patients ≥18 years, with known coronary artery anatomy (defined at coronary angiography performed within 3 months of recruiment) were considered eligible for the study. Exclusion criteria were left ventricular dysfunction (<45% left ventricular ejection fraction on a transthoracic echocardiogram), the presence of other cardiac diseases (eg primary valve disease or cardiomyopathies), acute coronary syndrome <3 months, uncontrolled hypertension, uncontrolled arrhythmias, third-degree left bundle branch block, pacemaker rhythm, stable angina classes III or IV, anemia (serum hemoglobin <12 g/dl), ≥50% left main coronary artery disease, chronic pulmonary disease or inability to exercise.

Significant CAD was considered as any ≥50% stenosis in a major epicardial coronary artery. Multivessel CAD was considered as the presence of significant CAD in ≥ 2 coronary arteries.

The research was approved by the institutional ethics committee and was performed in compliance with the 1975 Declaration of Helsinki. Informed consent was obtained from each subject.

Study protocol

All patients underwent CPET with radiotracer injection during exercise and myocardial perfusion scintigraphy on the same day. Antianginal medications were

stopped before the CPET (nitrates for 24 h, calcium antagonists and beta-blockers for 2 days). A symptom-limited CPET was performed on a treadmill (Ergo PC Elite, Micromed, Brasilia, Brazil). Heart rate and blood pressure were measured every minute during exercise and recovery. A 12-lead ECG was continuously evaluated and recorded every 3 minutes. After calibration of the volumes and gas exchange analyzers, patients breathed through a mask connected to a two-way respiratory valve. Expired gases and volumes were analyzed (VO_{2000}, MedGraphics, MN, EUA). All individuals underwent CPET with a ramp protocol (Balady et al, 2010). O2 pulse and O2 pulse curves were automatically obtained. The O2 pulse curves were interpreted by two experienced examiners who were blinded to clinical and MPS data and were classified as: A- normal; B- probably normal (normal slope with lower values); C- probably abnormal (flat and low); or D- definitely abnormal (descending slope) (Klainman et al, 2002). The agreement between observers, evaluated with kappa statistic, was 0.65 (CI 95% 0.39-0.66). The final interpretation of the curve pattern was defined by consensus. Sensitivity, specificity, positive and negative predictive values of the pattern of the PuO2 curves were assessed using the presence of angiographically defined CAD as the gold standard. For these analyses, normal or probably normal curves (A/B) were studied together. Similarly, probably abnormal or definitely abnormal curves (C/D) were grouped.

At near-maximal exercise, ^{99m}Tc-sestamibi (20-25 mCi) was injected intravenously, and exercise was continued at maximal workload for at least 1 minute. Exercise was terminated if there was increasing angina, a fall in blood pressure >20mmHg, limiting dyspnea or fatigue or sustained arrhythmias. Significant ST-segment depression was defined as that ≥1.5mm, horizontal or downsloping, 80 ms after the J-point. Up to 60 minutes after tracer injection, myocardial perfusion scintigraphy

was performed in an Infinia Hawkeye 4 camera (General Electric Healthcare, WI, EUA). Resting images were obtained on a separate day after injection of ^{99m}Tc-sestamibi (20-25 mCi). Perfusion scores were calculated and expressed the extent and severity of total, resting and ischemic perfusion defects (summed stress, rest and difference scores- SSS, SRS and SDS respectively) (Berman et al, 1995). Ischemia was considered present when the SDS was >1. Left ventricular ejection fraction (LVEF) was automatically obtained with QGS software (Cedars-Sinai Medical Center, Los Angeles, California, USA). Images were blindly interpreted by 2 experienced observers and the final results were defined by consensus.

Statistical analysis

Categorical variables, presented as frequencies with percentages, were compared using Fisher´s exact test or the chi-square test. Continuous variables, presented as mean ± SD or median and interquartile range, were compared using Student´s *t* test or Mann-Whitney´s *U* test, whenever appropriate. A logistic regression analysis was used to identify, among clinical, CPET and scintigraphic variables, those with an independent association with angiographically defined CAD. A value of $p<0.05$ was considered statistically significant in all analyses. Calculations were performed using R software, version 3.2.2.

Results

Patient characteristics, CPET and scintigraphic data are shown in Table 1. Fourteen patients (35.0%) had normal coronary arteries, 11 (27.0%) had single-vessel CAD and 15 (38.0%) had multivessel CAD. Table 2 depicts the comparison between patients with or without CAD. The former were older, had higher rates of diabetes,

smoking, hypercholesterolemia and stable angina, and more often used antiplatelet drugs, angiotensin-converting enzyme inhibitors and nitrates. Exercise duration was shorter, as well as peak heart rate, in patients with CAD. They also had a higher prevalence of ischemia, higher SSS and SDS.

Figure 1 shows examples of the four possible curve patterns. The evaluation of the diagnostic performance of the O2 pulse curves showed that there were 16 patients (40.0% of the total number of patients) with A/B curves and angiographically defined CAD (false-negatives). Eleven patients (27.5% of the total) had A/B curves and no CAD (true-negatives). Probably or definitely abnormal curves (C/D) were found in 10 patients with CAD (25.0% of the whole population were true-positives). Finally, C/D curves occurred in 3 patients without CAD (7.5% of false-positives). Interestingly, there was no association between ischemic ST-segment changes and the O2 pulse curve patterns (43.3% in A/B curves versus 30% in C/D curves, p=1)

Sensitivity, specificity, positive and negative predictive values of the O2 pulse curve pattern (considering the C/D patterns as abnormal O2 pulse and using the presence of angiographically defined CAD as the gold standard) were, respectively, 38.5%, 78.6%, 76.9%, and 40.7%. Additionally, the sensitivity, specificity, positive and negative predictive values of the C/D O2 pulse curve pattern for the diagnosis of multivessel CAD were, respectively, 29.4%, 65.2%, 38.5%, and 55.6%.

Of note, the concordance rate between the abnormal O2 pulse curve pattern and myocardial perfusion scintigraphy (considering only ischemic scintigraphic studies) was 38.1%. Abnormal curves without scintigraphic evidence of ischemia occurred in 5 patients, among whom 3 had large areas of fibrosis and documented CAD, and 2 had normal perfusion and no CAD. Normal curves with scintigraphic ischemia were found in 20 patients, 15 of them (75%) with CAD. Sensitivity, specificity, positive and

negative predictive values of the abnormal O2 pulse curve pattern (C/D) using the presence of myocardial ischemia defined by scintigraphy were, respectively, 61.5%, 31.0%, 28.6% and 64.3%. Figure 2 shows an example of a patient with 3-vessel CAD, abnormal O2 pulse curve and myocardial scintigraphy without ischemia, but with a large nonreversible perfusion defect, indicating myocardial fibrosis.

In the logistic regression analysis, the final ajusted model showed that age and the SSS were significantly associated with the presence of CAD, such that for each year of increasing age and for each unit of the SSS, the chance of having CAD increased 18% and 27%, respectively (Table 3). Abnormal O2 pulse curve patterns (B or C or both combined) were not independently associated with CAD at coronary angiography.

Discussion

Cardiopulmonary exercise testing (CPET), with measures such as oxygen uptake and oxygen pulse, provides objective and reproducible indices that may be used for diagnostic and prognostic evaluation of cardiovascular disease. Indeed, CPET is an important non-invasive tool, while usually not employed to its full clinical potential. Reasons for that may include limited availability of the equipment or of trained personnel, but also the paucity of information upon its diagnostic usefulness, especially regarding CAD. This study therefore evaluated the diagnostic application of CPET for CAD assessment, using the pattern of the O2 pulse curve as an indicator of exercise-induced ischemia, compared to the detection of ischemia by myocardial perfusion scintigraphy and to the objective evidence of CAD at coronary angiography.

In this study, all participants had documented coronary artery anatomy, defined by invasive coronary angiography. This is a major strength, as most published data on the value of the O2 pulse curve do not have coronary artery anatomy data for

comparison (Klainman et al 1996; Belardinelli et al, 2003). Belardinelli et al (2003) have evaluated the diagnostic accuracy of the O2 pulse in patients with known CAD, but the control group was comprised of supposedly healthy individuals, without a confirmation of normal coronary arteries. In our series, patients had a distribution of CAD severity of approximately 1/3 of normal coronary arteries, 1/3 of single-vessel CAD and 1/3 of multivessel CAD, an optimal model for the assessment of the diagnostic properties of a noninvasive method. It may be intriguing that a third of the patients who underwent coronary angiography had normal coronaries, but that might be explained as the exam had been indicated by assisting physicians, who might have ordered the test due to persistent anginal symptoms, ischemic exercise tests (with ST-segment criteria for ischemia), equivocal or even abnormal myocardial perfusion scintigraphy results.

The diagnostic performance of the O2 pulse curves using CAD detected at coronary angiography as the gold standard showed that sensitivity was very low, as well as the negative predictive value, while specificity and the positive predictive value were good or reasonable. This indicates a problem of the O2 pulse curve patterns both to detect disease when present, as well as to exclude it when absent. Interestingly, when considering the presence of multivessel CAD, what theoretically would increase the ischemic burden and facilitate ischemia detection by the PuO2 curve patterns, the sensitivity was indeed reduced, while the other remained unchanged or were also reduced.

The comparison of a functional test (CPET, with its variables such as the O2 pulse) with an anatomic test (coronary angiography) may be viewed as inadequate, even with coronary anatomy being, for decades, the gold standard for all noninvasive diagnostic tests. So we compared the O2 pulse curve pattern to the results of myocardial

perfusion scintigraphy, both functional tests. The concordance rate between the O2 pulse curve pattern and myocardial perfusion at peak exercise was low- slightly over 30%. This was a peculiar finding, as the PuO2 abnormality was expected to correlate with myocardial ischemia, according to previous data (Belardinelli et al, 2003; Muñoz et al, 2007). It should be noted, though, that for this study, only ischemic scintigraphic studies were used to define a "positive" scintigraphy. Discordances considered as the absence of scintigraphic ischemia in patients with abnormal O2 pulse curves (which were found in 5 patients) were in 40% of the cases due to truly "false-positive" curves (when both scintigraphy and coronary angiography were normal), but in 60% of the patients might be attributed to the definition of "abnormal" scintigraphy used in this study- the presence of ischemia. In fact, these patients had large areas of fibrosis without ischemia, and O2 pulse curves were abnormal. So, as further indicated by other data from our study, the underlying mechanism of the O2 pulse abnormality is probably chronic left ventricular myocardial dysfunction-even in the absence of a reduced left ventricular ejection fraction.

The fact that the occurrence of exercise-induced myocardial ischemia does not seem to be intrinsically associated with the O2 pulse abnormality is also suggested by the 20 patients who had "negative" (normal or probably normal) curves with scintigraphic ischemia, 75% of whom had angiographically documented CAD. It is worth noting that most of these patients (12 out of 15) had 1 or 2-vessel CAD, what might suggest a reduced ability of the O2 pulse curve to identify patients with small to moderate amounts of ischemia. This is in line with the results of Munoz et al (2007), who only found abnormal O2 pulse curves in patients with extensive ischemia. The multivariable analysis corroborated the initial findings, showing that the total amount of perfusion defect (and not the presence or extent of ischemia) and the abnormal O2 pulse

curve patterns (B or C or both combined) were not independently associated with angiographically confirmed CAD.

Limitations

This study is limited by the small sample size. Larger patient number would enable further inferences, such as the evaluation of the effect of different severities of coronary artery obstruction, of different coronary anatomies (eg, left anterior descending versus right coronary artery), or of lesion location (proximal versus distal) on the pattern of the O2 pulse curve. With the current patient sample, only the number of coronary arteries with significant lesions could be used for evaluation.

Conclusions

The O2 pulse curve pattern has low sensitivity and negative predictive value for the diagnosis of obstructive CAD. Abnormal O2 pulse curve pattern was not associated with myocardial ischemia defined by scintigraphy; the mechanism underlying the O2 pulse abnormality most likely is myocardial dysfunction, even if global left ventricular function is not compromised, as the extent of global perfusion defect was significantly associated with abnormal O2 pulse curve patterns.

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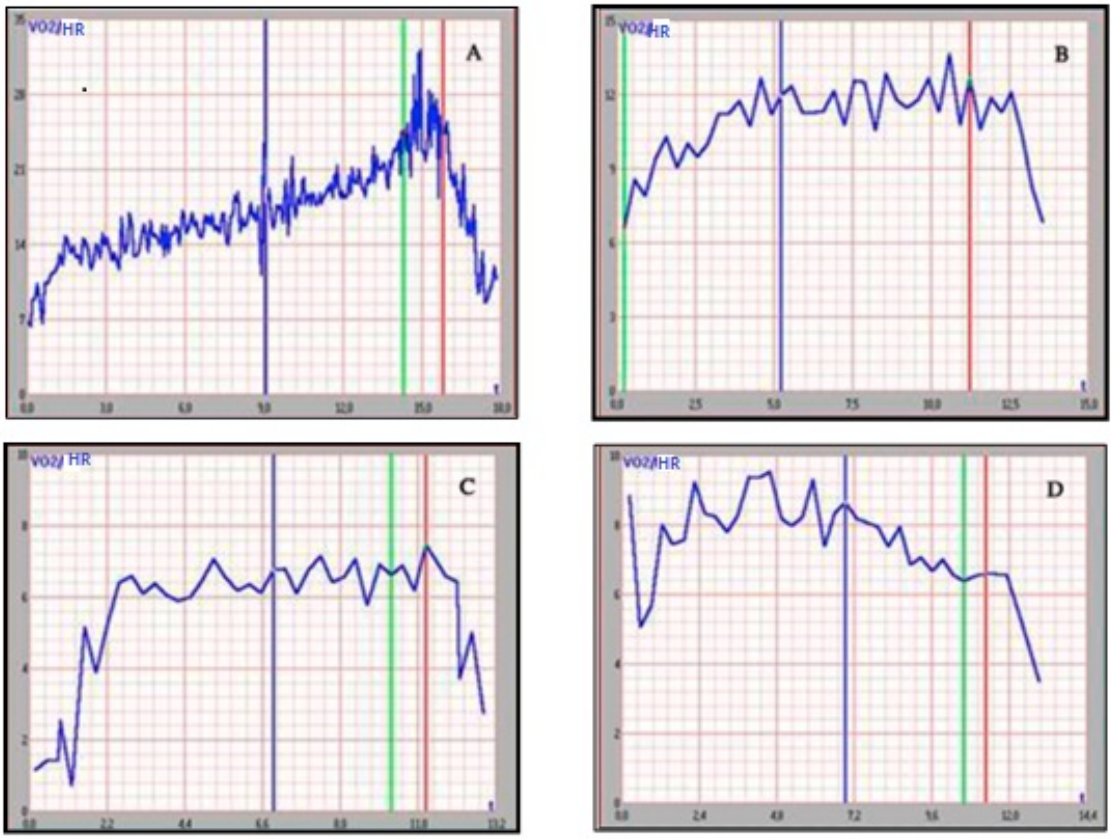

Figure 1. Examples of O2 pulse curves. A, normal curve. B, probably normal curve. C, probably abnormal curve. D, definitely abnormal curve

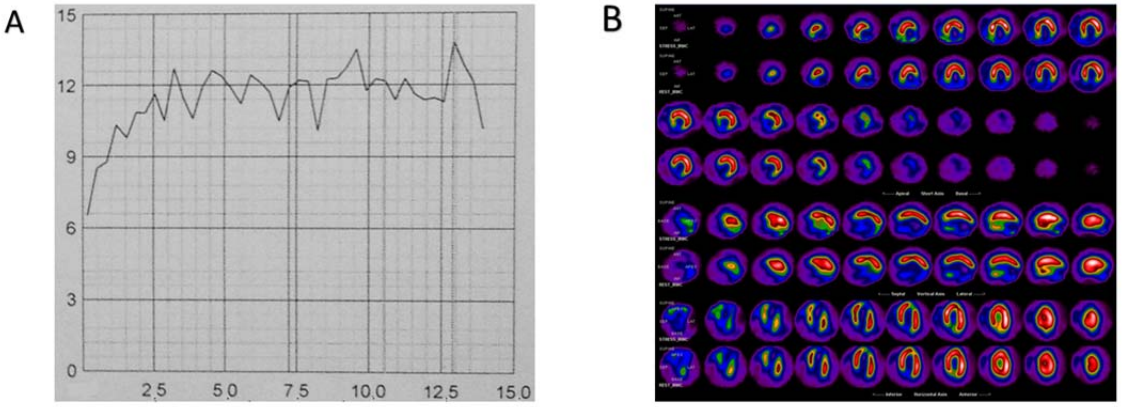

Figure 2. A 60- year old woman with stable angina, prior myocardial infarction and coronary angiography showing 70% left anterior descending, 70% left circumflex and 100% right coronary artery obstructions.

A: flat O2 pulse curve, with probably abnormal (C) pattern. X axis: time (minutes). Y axis: oxygen consumption in ml/heartbeat (VO2/beat)

B: stress/rest myocardial perfusion scintigraphy showing a large, nonreversible apical and inferior wall defect.

Table 1. Demographic, clinical, CPET and scintigraphic data

	N (%) or mean±SD
Age (years)	57.0 ± 9.6
Male	24 (60.0)
Body mass index (kg/m^2)	27.5 ± 4.5
Hypertension	34 (85.0)
Diabetes	9 (22.5)
Stable angina	25 (62.5)
Prior myocardial infarction	19 (47.5)
Medications	
Beta-blockers	27 (67.5)
Antiplatelets	33 (82.5)
Statins	28 (70.0)
Angiotensin-converting inhibitors	39 (97.5)
Calcim channel antagonists	13 (32.5)
Nitrates	18 (45.0)
Coronary angiography	
Normal coronary arteries	14 (35.0)
Single-vessel	11 (27.0)
Multivessel	15 (38.0)
Hemoglobin (g/dl)	13.8 ± 1.3

CPET, cardiopulmonary exercise test

Table 2. Comparisons between patients with or without coronary artery disease (CAD)

	With CAD (n=26)	Without CAD (n=14)
Demographic and clinical data		
Age (years)	59.5 ± 10.0	53.0 ± 6.6 *
Male	18 (69.2%)	6 (42.8)
Body mass index (kg/m^2)	27.6 ± 3.7	27.3 ± 5.8
Hypertension	22 (84.6)	12 (85.7)
Diabetes	9 (34.6)	0 *
Hypercholesterolemia	22 (84.6)	7 (50.0)*
Smoking†	23 (88.5)	9 (64.2)*
Stable angina	23 (88.5)	2 (14.3)*
Beta-blocker	20 (76.9)	7 (50.0)
Antiplatelet agents	24 (92.3)	9 (64.2)*
Statins	20 (76.9)	8 (57.1)
Angiotensin-converting enzyme inhibitors	11 (42.3)	1 (7.1)*
Calcium channel blockers	9 (34.6)	4 (28.6)
Nitrates	15 (57.6)	3 (21.4)*
CPET		
Exercise duration (min)	7.8 ± 3.2	9.7 ± 1.5*
ST depression	12 (46.1)	4 (28.5)
Peak heart rate (bpm)	137.0 ± 16.6	151 ± 20.4 *
% maximal predicted heart rate	85.7 ± 11.9	90.6 ± 11.6
Heart rate recovery (bpm)	18.5 ± 10.0	19.6 ± 7.9
Peak systolic blood pressure (mmHg)	176.0 ± 28.0	186.0 ± 28.9
O2 pulse curve pattern		
A	5 (19.2)	3 (21.4)
B	11 (42.3)	8 (57.1)
C	8 (30.8)	3 (21.4)
D	2 (7.7)	0
VO2 max	18.4 ± 5.9	21.8 ± 4.8
Myocardial perfusion scintigraphy		
SSS	13.4 ± 9.3	4.6 ± 4.9 *
SRS	6.7 ± 8.6	3.0 ± 4.2
SDS	6.6 ± 6.3	1.6 ± 2.3 *
Ischemia	23 (88.5)	4 (28.5)*
Post-stress left ventricular ejection fraction(%)	52.5 ± 13.8	55.0 ± 10.0

* $p<0.05$

† defined as current or former smoking

CAD, coronary artery disease; CPET, cardiopulmonary exercise test; O2 pulse, oxygen pulse; SSS, summed stress score; SRS, summed rest score; SDS, summed difference score; VO2 max, maximal oxygen consumption

Table 3. Logistic regression for the association of clinical, exercise and scintigraphic variables with the presence of CAD

	Unadjusted		**Adjusted (final model)**	
	Odds ratio	**95% CI**	***Odds ratio***	**95% CI**
Female gender	0.33	-1.01 – 1.68	-	-
Age	1.08	1.0 – 1.16	1.18	1.06 – 1.30
Hypercholesterolemia	5.49	4.0 – 6.99	-	-
Peak heart rate	0.95	0.91 – 0.99	-	-
SSS	1.18	1.06 – 1,32	1.27	1.12 – 1.44
SDS	1.45	1.14 – 1.76	-	-

All results shown have p values <0.05

SDS, summed difference score; SSS, summed stress score