The Relationship Between Left Ventricular Function Assessed by Multigated Radionuclide Test and Cardiopulmonary Exercise Test in Patients With Ischemic Heart Disease*

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Study objectives: To compare the oxygen pulse curve (O₂P-C) as measured during cardiopulmonary exercise testing (CPET) with left ventricular (LV) ejection fraction (LVEF) rest-exercise response as measured by multigated equilibrium ⁹⁹ᵐTc radionuclide cineangiography (MUGA) in patients with different degrees of ischemic heart disease (IHD).

Patients: Forty-six patients (39 men and 7 women; mean ± 1 SD age, 59.2 ± 11 years) with IHD, with no hypertrophic, valvular, or pericardial disease.

Methods: A supine bicycle ergometer with increments of 25 W every 2 min was used for MUGA, and an electronically braked cycle ergometer was used for upright symptoms-limited CPET. Exercise was increased by 10 to 20 W/min until the target heart rate (HR) was reached (similar peak HR for both studies).

Measurements and results: The O₂P-C was scored on a 10-point scale as follows: type A, normal curve (10 points); type B, normal-shaped curve with low values (8 points); type C, low and flat curve (5 points); type D, descending curve (3 points). Findings for the MUGA study were classified into four groups by the degree of ischemic response: group 1 (control), normal diastolic function (n = 10), LVEF > 55%, LVEF during exercise minus LVEF at rest [ΔLVEF] ≥ 5%; group 2, mild ischemia (n = 10), LVEF > 55%, < 0 ΔLVEF < 5%, diastolic dysfunction at exercise (prominent “A” waves); group 3, LV dysfunction (n = 9), LVEF ≤ 35% at rest; and group 4, significant ischemia (n = 17), LVEF > 55%, ΔLVEF < 0, diastolic dysfunction. A highly significant relationship between the O₂P-C score and the MUGA grouping was observed by Fisher’s Exact Test and Pearson’s linear regression line (p < 0.001; R = −0.89).

Conclusions: Exercise-responded O₂P-C might serve as a good noninvasive, physiologically based, parameter to distinguish between IHD patients with normal and impaired LV function.

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Key words: cardiopulmonary exercise test; coronary artery disease; left ventricular ejection fraction; multigated equilibrium radionuclide cineangiography; oxygen pulse

Abbreviations: CAD = coronary artery disease; CPET = cardiopulmonary exercise testing; EDV = end-diastolic volume; HR = heart rate; IHD = ischemic heart disease; LV = left ventricular; LVEF = left ventricular ejection fraction; ΔLVEF = left ventricular ejection fraction during exercise minus left ventricular ejection fraction at rest; MUGA = multigated equilibrium ⁹⁹ᵐTc radionuclide cineangiography; O₂P = oxygen pulse; O₂P-C = oxygen pulse curve; SV = stroke volume VO₂ = oxygen consumption

The assessment of left ventricular (LV) performance during exercise is an important part of the evaluation of patients with ischemic heart disease (IHD). LV function can be estimated by measuring LV ejection fraction (LVEF) at rest and during exercise with semi-invasive multigated equilibrium ⁹⁹ᵐTc radionuclide cineangiography (MUGA). In healthy individuals, LVEF as well as stroke volume (SV) usually increase during exercise; however, in patients with impaired LV function, LVEF and SV remain constant or decrease.¹⁻³ Recently, we have shown that the addition of a prominent A-wave to a normal systolic response during exercise⁴⁻⁵ raises the sensitivity of MUGA to detect coronary artery disease (CAD).
Noninvasive cardiopulmonary exercise testing (CPET) is an adjunctive clinical tool to MUGA used for the assessment of overall metabolic-cardiovascular-ventilatory coupling. The extraction of physiologic data on oxygen consumption (VO$_2$), carbon dioxide production, heart rate (HR) and oxygen pulse (O$_2$P) on CPET provide an objective estimate of the functional reserve of the heart.$^{6-8}$

According to the Fick formula, O$_2$P (VO$_2$/HR) is directly related to SV. In earlier studies,$^9,10$ our team defined a scale for scoring the appearance of the O$_2$P curve (O$_2$P-C) during CPET in patients with different degrees of IHD, with normal or impaired LV function. Since similar exercise conditions should yield a similar cardiac dynamic response, we speculated that the quantitative LVEF by MUGA should correspond to the O$_2$P-C score by CPET. The purpose of the present study was to test this hypothesis in patients with different degrees of IHD or with LV dysfunction.

**Materials and Methods**

**Patients**

Forty-six patients (39 men and 7 women; mean ± 1 SD age, 59.2 ± 11 years; range, 37 to 77 years) with CAD volunteered to participate in the study. None had LV hypertrophy or valvular or pericardial disease. In all cases, MUGA exercise study was followed by CPET within 2 to 3 weeks. CAD was confirmed by coronary angiography. Medications were stopped 24 h prior to all tests. Before undergoing MUGA, the patients provided written informed consent.

**Exercise Tests**

MUGA: MUGA was performed to determine LVEF at rest and at peak exercise. A supine bicycle ergometer with increments of 25 W every 2 min was used; patients were asked to continue until the predefined endpoint was reached (appearance of symptoms, or volitional fatigue, or attainment of a target HR). Prior to the study, stannous pyrophosphate, 10 mg, was injected, followed 15 min later by 20 to 25 mCi of $^{99m}$Tc. Data were recorded with a small-field-of-view scintillation camera and digital processor; the camera was interfaced to an intertechnique cine data system (APEX-SP409; Elscint; Haifa, Israel). The detector was located in the 45° left anterior oblique projection. The cardiac cycle was divided into 24 frames yielding an average time per frame of 20 to 30 ms. Calibration was set to 4,000 kilo counts for rest and exercise for all frames; 2,000 kilo counts were used at exercise. After acquisition at rest, the study was repeated during supine exercise until peak load was reached. The workload was then immediately decreased by 50% to allow the patient’s upper body to remain as immobile as possible, with a stable uniform R-R interval on the ECG, and ventricular scintigraphy was started. This procedure was based on the assumption that if an ischemic response is observed during exercise, recovery is not expected during the short recording time after peak exercise.

Patients were classified into four groups according to the

![Figure 1. The four O$_2$P-C variables. Top left, a: normal curve (10 points); top right, b: normal shape, low values (8 points); bottom left, c: flat curve with low values (5 points); bottom right, d: descending curve (3 points). Dashed curve refers to HR response. Continuous curve refers to the O$_2$P response (VO$_2$/HR). Dash-dot (horizontal) line refers to predicted O$_2$P values.](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21974/ on 06/25/2017)
degree of ischemic response: group 1 (n = 10, control), normal findings, defined as LVEF > 55%. LVEF during exercise minus LVEF at rest (ΔLVEF) ≥ 5%, normal diastolic function (ie, normal A wave); group 2 (n = 10), mild ischemia, LVEF > 35%, 0% < ΔLVEF < 5%, prominent A wave (ie, diastolic dysfunction); group 3 (n = 9), LV dysfunction, LVEF ≤ 35% at rest; and group 4 (n = 17), significant ischemia, LVEF > 55%, ΔLVEF < 0%, prominent A wave.4

CPET: Upright, symptoms-limited CPET was performed on an electronically braked cycle ergometer (Ergoline 800S, D7474; Ergoline GmbH; Bitz, Germany). Exercise was initiated at 20 W and increased thereafter by 10 to 20 W/min until target HR was reached (ie, HR similar to the maximum HR reached in the MUGA study). Cardiopulmonary data were collected by an on-line metabolic cart (CPX Medical Graphics; St. Paul, MN).Expired fraction of oxygen (zirconium fuel-cell sensor) and carbon dioxide (infrared absorption) and the rate of air flow were measured at rest by a metabolic analyzer and linearized pneumotachometer and, during the exercise period, by a breathing apparatus consisting of a low-resistance two-way valve (dead space, 100 mL; Hans Rudolph; Kansas City, MO). The breath-by-breath signals were integrated by computer to yield 30-s averages of HR, minute ventilation, VO2, carbon dioxide production, and O2P. Peak VO2 was the highest VO2 achieved during exercise. BP was measured with a cuff sphygmomanometer at the beginning and end of each stage. A 12-lead ECG (Cardiofax; Nihon Kohden; Tokyo, Japan) was recorded at rest following a 2-min warm-up and every minute during the test. One precordial lead (V5) was monitored continuously (VC-22; Nihon Kohden).

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Grading was blinded for both MUGA and O2P-C. Medication regimens, exercise HRs, and target peak HRs were similar in the MUGA and CPET studies. For the purpose of this study, patients maintained their regular medication regimen.

Statistics

To analyze the statistical significance of the relationship between the distribution of patients by MUGA findings and O2P-C score, Fisher’s Exact Test was used. We also used Pearson’s linear regression test to correlate between the two methods. A p value < 0.05 was considered statistically significant. All statistical analyses were performed with statistical software (Statistical Analysis Software, version 6; SAS Institute; Cary, NC).12 All values are presented as mean ± 1 SD.

RESULTS

Table 1 shows the patient characteristics and preliminary data by group; no significant differences were found for age, height or weight. Table 2 shows the results of CPET. A significant gradual reduction in peak VO2, maximal O2P, and O2P-C score was noted from group 1 (normal) to group 2 to groups 3 and 4 (p < 0.05 to 0.01). Comparison of group 3 and group 4 yielded no significant differences in VO2 peak or O2P. However, the O2P-C scores were 5.5 ± 1.4 and 4.1 ± 0.9, respectively (p < 0.05), and it was the relationship of this parameter to the MUGA exercise response that was studied here. The MUGA exercise test results, as shown in Table 3, reveal good LV function at rest in groups 1, 2, and 4, with no significant differences among them. Never-
Table 4—Relationship Between MUGA Grouping and $O_2P-C$ Score*  

<table>
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<tr>
<th>MUGA Grouping</th>
<th>O$_2$P-C Scores</th>
<th>Group 1 (n = 10)</th>
<th>Group 2 (n = 10)</th>
<th>Group 3 (n = 9)</th>
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*Data in MUGA grouping columns indicate no. of patients (p < 0.001).

Discussion

MUGA is considered a clinically reliable test for the assessment of systolic and diastolic LV response during exercise in patients with ischemia.$^{4,5,13}$ It has, however, several limitations: maximum HR is lower in the supine position; a constant maximum HR is difficult to maintain during exercise-LVEF recording, and body movements during exercise may cause technical problems.

In the present study, to determine if the $O_2P-C$ is a reliable noninvasive parameter of changes in LV function during the ischemic response to exercise, we compared the $O_2P-C$ to the MUGA LVEF findings during exercise. Our hypothesis was based on the rationale that both the LVEF and the $O_2P$ are influenced directly by the SV response to exercise, and therefore might correlate. Furthermore, the $O_2P$ response to exercise is easily obtained and may serve as an important additional assessment of cardiac function.

At the same time, it should be emphasized that these two parameters have some physiologic differences. The LVEF represents the percentage change between the end-diastolic (EDV) and end-systolic volume (ie, SV), divided by the EDV (SV × 100/EDV). The $O_2P$ relates directly to the SV (ie, Fick formula) and the difference between the arterial and venous oxygen content. The $O_2P$ is a good noninvasive index of the physiologic efficiency of oxygen transport. $O_2P$ is lower in patients with heart disease than in healthy adults, apparently owing to the decrease in SV secondary to the LV dysfunction due to infarction or ischemia.$^{11,14}$

In the present study, we found that the MUGA, as
classified by exercise response, was significantly correlated with the $O_2P-C$ score according to the Fisher’s Exact Test (Table 4) and Pearson’s linear regression (Fig 2). In our earlier study, we demonstrated a correlative response during exercise between peak $O_2P$ and $\Delta$LVEF in normal individuals (group 1), patients with silent ischemia (group 2), and patients with symptomatic ischemia (group 3). The peak $O_2P$, as well as the $\Delta$LVEF, decreased gradually from group 1 to group 3. In two other studies, we demonstrated that both exercise training and percutaneous transluminal angioplasty significantly improve the $O_2P$ continuous response, scored like in the present study, during exercise.

The present study demonstrates the possible physiologic meaning of the $O_2P-C$ score, which showed a significant correlation with the LVEF at rest and the $\Delta$LVEF response at exercise. Group 1 (control) demonstrated normal LVEF at rest (59.6 ± 6.9%) and normal $\Delta$LVEF response at exercise (6.4 ± 3.1%), which correlated well with the normal-shaped $O_2P-C$ (score, 10 points). Group 2 had normal LVEF at rest (58.5 ± 4.8%) but a mild ischemic response ($\Delta$LVEF of 3.1 ± 2.2%) and diastolic impairment of the LV filling curve at exercise, which correlated well with the 8-point curve score. The scoring variation in this group fits the possible functional variations in patients with mild ischemia, with some demonstrating normal functional indexes and others demonstrating significant LV dysfunction during exercise. Group 3 had LV dysfunction (LVEF at rest of 26.8 ± 7.6%) with no significant ischemic response during exercise. This correlated well with the flat $O_2P-C$ response (score, 5 points). The flat curve means a constant or decreasing SV response during exercise, as expected in patients with LV dysfunction. Group 4 had good LV function at rest but a significant ischemic response during exercise (LVEF, −5.3 ± 4%), which correlated with the descending $O_2P-C$ (score, 3 points). A descending curve represents a drop in SV, since the ischemic response becomes significant toward the peak exercise.

We conclude that the exercise $O_2P-C$ might serve as a good noninvasive, physiologically based parameter for the evaluation of ischemic patients to distinguish between good or impaired LV function. More intensive and extensive investigations are needed to further confirm these findings.

**REFERENCES**