The impact of combined cardiopulmonary exercise testing and SPECT myocardial perfusion imaging on downstream evaluation and management

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Objective. **The diagnostic yield of combined cardiopulmonary exercise testing (CPET) and myocardial perfusion imaging (MPI) in patients referred for stress testing has received limited study.**

Methods. **We evaluated consecutive patients who underwent combined CPET-MPI at a single tertiary referral center between 2011 and 2015. An abnormal CPET was defined as any of the following: reduced oxygen consumption, cardiac output impairment, or pulmonary impairment. Normal MPI was defined as the absence of resting or stress perfusion defect. The primary study outcome was change in clinical decision-making after CPET-MPI including management of pulmonary disease, management of deconditioning, heart failure management, and referral for cardiac catheterization. Outcomes of patients with normal and abnormal MPI were presented based on the specific CPET abnormality.**

Results. **415 patients were included in the study. Of the 269 patients that had normal MPI, 206 (77%) had abnormal CPET. Patients with abnormal CPET and normal MPI, compared with patients that had normal CPET and normal MPI, were more frequently diagnosed with pulmonary disease (11.7% vs 3.2%, $P = .04$) and deconditioning (33.5% vs 17.4%, $P = .01$). Of the 146 patients that had abnormal MPI, 128 (88%) had abnormal CPET. Patients with abnormal CPET and abnormal MPI, compared with patients that had normal CPET and abnormal MPI, did not statistically differ with regard to the study outcome.**

Conclusion. **An abnormal CPET, if the MPI was normal, prompted further evaluation and led to management of pulmonary disease and deconditioning. (J Nucl Cardiol 2019;26:92–106.)**

Key Words: Myocardial perfusion imaging • cardiopulmonary testing • clinical outcomes

Abbreviations			
CPET	Cardiopulmonary exercise testing	VO_2	Oxygen consumption
MPI	Myocardial perfusion imaging	VE	Minute ventilation
SPECT	Single-photon emission computed tomography	VCO_2	Carbon dioxide production
MET	Metabolic equivalents	RER	Respiratory exchange ratio
FAC	Functional aerobic capacity		

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INTRODUCTION

Among patients referred for stress testing, if patients are able to exercise, standard exercise treadmill testing (ETT) is usually performed in conjunction with single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI). Although infrequently, cardiopulmonary exercise testing (CPET) can be combined with MPI to evaluate patients referred for stress testing. CPET has the advantage of differentiating cardiac diagnoses from pulmonary conditions while providing additional prognostic information on both cardiac and pulmonary function.[1] Objective measurements during CPET such as peak aerobic capacity (peak VO_2) and ventilatory efficiency (VE/VCO_2) correlate closely with peak cardiac output and are important prognostic markers. These and other measurements during CPET may also be useful in guiding patient management.[2–7] SPECT MPI, on the other hand, has traditionally been used for more focused assessment of suspected or known coronary artery disease (CAD). As such, SPECT MPI and CPET may provide complementary diagnostic and prognostic information in the evaluation of patients referred for stress testing. This is important, as many of these patients have vague chest symptoms, dyspnea, and/or other non-specific limitations.[8] Their presentation may be due to underlying CAD, other cardiac diagnoses, pulmonary disorders, heart failure, deconditioning, or a combination of these conditions. Although anticipated, it is not known whether combining CPET with SPECT MPI increases the diagnostic yield of the studies and affects the downstream evaluation of such patients. The objective of the current study was to determine if the addition of CPET to SPECT MPI alters clinical decision-making.

METHODS

Patient Population

The Nuclear Cardiology Laboratory at Mayo Clinic in Rochester, Minnesota, began offering combined CPET/SPECT MPI in January of 2011 as a standard clinical study. From January 2011 to December 2015, 435 consecutive patients underwent combined CPET-MPI. Inclusion criteria were patients who were clinically referred for CPET/MPI testing at a single institution and had given consent for their records to be included in research studies. CPET and MPI referral was at the clinical discretion of the physician. In about 25% of the patients, the tests were ordered separately, and the referring providers were contacted and gave permission to combine the tests. Among this group of 435 patients, 18 patients did not provide research authorization and two patients had incomplete SPECT and/or CPET data and were therefore excluded. Therefore, a total of 415 patients were included in the study. Baseline demographic data and medical history were collected retrospectively, whereas test results and additional patient evaluation and outcomes post CPET/MPI were recorded prospectively. On some occasions, patients received a consultation at our medical center but then received additional testing or intervention at another institution. In those cases where medical records were not available, patients were reported to have missing data and downstream evaluation was based on the documentation of the consulting physician at our medical center. All patients included in the study provided research authorization. The Mayo Clinic Institutional Review Board approved the study.

Combined CPET and SPECT MPI Protocol

Patients fasted for two hours prior to the procedure but were continued on their daily medication regimen. Each patient underwent symptom-limited graded treadmill testing ($n = 410$) or lower extremity bicycle ergometry ($n = 5$) with continuous electrocardiographic monitoring and breath-by-breath gas exchange analysis consisting of 2-minute stages with 2-metabolic equivalent (MET) increases per stage. Blood pressure, electrocardiography, and continuous pulse oximetry were monitored during the testing period. Metabolic equivalents were defined as 1 MET = 3.5 mL/kg/min of oxygen consumption and estimated based on exercise time.[9] Functional aerobic capacity (FAC) was calculated as achieved METs/predicted METs with predicted METs dependent upon age and sex.[9] An appropriate heart rate response was defined as the ability to achieve 85% of the age-predicted maximal heart rate.[10] An abnormal heart rate recovery was defined as a $\leq$12 beats per minute decrease in the heart rate in the first minute of active recovery.[11] Ischemic and non-diagnostic electrocardiographic criteria are as previously described.[12] A hypertensive response to exercise was defined as a systolic blood pressure >210 mmHg in males and >190 mmHg in females.[13] A hypotensive response to exercise was defined as a decline in systolic blood pressure below resting value or an initial increase during early exercise followed by a decrease of $\geq$10 mmHg.[14,15] A blunted heart rate response to exercise was defined as an increase of maximal heart rate during exercise less than 1.20 times the baseline heart rate.[16] Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) were

measured throughout the testing period as previously described.[10] Predicted VO_2 max for males was calculated as 60 − (0.5 × age) mL/kg/min, whereas for females was calculated as 48 − (0.4 × age) mL/kg/min. Ventilatory efficiency was calculated as the minimum ratio of VE/VCO_2 during exercise (VE/VCO_2 nadir) with normal values <35 (up to 40 for older patients). A normal respiratory exchange ratio (RER) was defined as >1.15 and a normal breathing reserve (BR) was defined as between 15 and 40%.[17] Pulmonary impairment was defined as a low VO_2 max with a rise over time, a respiratory exchange ratio (RER) <1.15, a BR <10%, a high VE/VCO_2, a low O_2 pulse with a rise vs time, and generally O_2 saturations <90% (varying dependent on type of pulmonary disease).[17] Cardiac output impairment was defined as a low rise in VO_2 max (defined as a flat rather than linear response of VO_2 with workload [17]), a RER >1.15, a BR >40%, a normal or high VE/VCO_2, a low O_2 pulse with a flat rise vs time, and normal or reduced O_2 saturations. Deconditioning was defined as a low VO_2 max with a rise over time, a RER >1.15, a BR between 25 and 60%, a normal VE/VCO_2, a low O_2 pulse with a rise over time, and O_2 saturations >90%.[17] Poor effort was defined as a low VO_2 max with a rise over time, a RER <1.15, a BR >40%, a normal VE/VCO_2, a low O_2 pulse with a rise over time, and oxygen saturations >90%.[17]

A one-day rest/stress SPECT technetium-99m (^{99m}Tc) sestamibi protocol was performed in conjunction with the CPET. At rest, 555 MBq to 1.11 GBq (8-10 mCi) of ^{99m}Tc sestamibi was injected intravenously. Thirty to 45 min following injection, resting images were acquired using the D-SPECT camera (Spectrum Dynamics, Haifa, Israel) in the semi-supine position. Specifically, images were obtained as each of the 9 pixelated detector columns rotated along its vertical axis and scanned the region of myocardium which was chosen by the user. Images were acquired with the Acquisition Optimization Time to achieve 1 million counts in the myocardium (reference). Post-stress gated image acquisition was performed using 16 frames per cardiac cycle. Resulting data obtained from each detector were subsequently stored in a 16 × 64 matrix with data from all 9 detectors combined for final image reconstruction. Emission data were collected via 9 low-energy, tungsten hole collimators and images were acquired using a standard 20% energy window centered on the 140 keV photopeak of ^{99m}Tc. At peak exercise during CPET, 24-40 mCi of ^{99m}Tc sestamibi was injected and repeat image acquisition was performed in the semi-supine position in a similar manner as described for the rest acquisition. Additionally, images were also acquired in the upright position in a similar manner as described for the rest acquisition. Studies were processed using Spectrum Dynamics proprietary reconstruction algorithms (QPS, Cedars-Sinai Medical Center, Los Angeles) utilizing a Spectrum Dynamics workstation. The reconstruction algorithm utilized the maximum-likelihood expectation maximization (MELM) method with resolution recovery, 4-7 iterations and 32 subsets. Additionally, kernel convolution smoothing filter (Gaussian) was used on transaxial data. Attenuation or scatter correction was not applied. Left ventricular ejection fraction (LVEF) was automatically calculated utilizing QGS programing.[18]

Rest and stress images were displayed in three standard planes (short-axis, horizontal long-axis, and vertical long-axis) and divided into 17 segments.[19] Images were interpreted by a consensus of two experienced observers using a standard 5-point semi-quantitative scale (0 = normal perfusion, 1 = mildly diminished, 2 = moderately diminished, 3 = severely diminished, and 4 = absent) along with a written description of the study as being a normal study, or an abnormal study with a fixed or reversible defect suggestive of infarction or ischemia, respectively, or both (partial viability). A defect present on the stress semi-supine position but not present on the upright position or vice versa was considered an artifact and was interpreted as being a normal study (i.e., interpreted as having no defect).

Data Analysis

Cases were grouped based on the results of MPI (presence or absence of perfusion defect) and were subsequently classified based upon whether they had abnormalities on CPET or not. All defects on MPI (reversible or not) were considered abnormal. CPET results were grouped based on whether pulmonary impairment was present, cardiac output impairment was present, or VO_2 was decreased. If any of those variables were abnormal, CPET was considered abnormal. The outcome of interest was clinical decision-making, which included (1) management of pulmonary disease, (2) management of deconditioning, (3) management of coronary disease, or (4) management of heart failure. (1) Management of pulmonary disease included the addition of inhaler therapy, referral to pulmonary medicine, including evaluation for sleep apnea, and/or referral for pulmonary function tests (PFTs) within a month of the consultation. (2) Management of deconditioning was defined as recommendations for lifestyle modifications in the form of weight loss, exercise counseling, or referral to cardiac rehabilitation at the time of the consultation. (3) Management of coronary artery disease was defined as referral to coronary angiogram, percutaneous coronary intervention, or coronary artery bypass grafting. We did not include medications for coronary disease as part of the

outcome since adjustment of those medications occurs on the basis of angina rather than results of exercise testing. (4) Management of heart failure included heart failure medication changes (addition, removal or dose adjustment of b-blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, aldosterone antagonists, and diuretics at the time of the consultation), referral for an automatic implantable cardioverter-defibrillator placement, or cardiac resynchronization therapy within a month of the consultation.

Statistical Analysis

Continuous variables were presented as means and standard deviation or median and interquartile range and compared using Student's *t* test or Wilcoxon rank-sum test, as appropriate. Categorical variables were presented as percentages and compared with the Chi-square test or Fischer's exact test, as appropriate. For the multivariable analysis, baseline demographics and parameters of the CPET and SPECT imaging were included in the univariable part. Subsequently, variables with an association of $P < .10$ were included in the multivariable model. A P value of <0.05 was considered statistically significant for all analyses. All analyses were performed with JMP software, version 9.0 (SAS Institute, Cary, North Carolina).

RESULTS

415 patients were included in the study. In the overall sample, mean age was 64 ± 12 years, 64% of the patients were male, body mass index (BMI) was 30 ± 8, 49% of the patients had prior diagnosed CAD (28% with prior percutaneous coronary intervention [PCI] and 16% with prior coronary artery bypass graft surgery [CABG]), 30% had a history of congestive heart failure (systolic or diastolic), 7% had diagnosed chronic obstructive pulmonary disease or interstitial lung disease, and 19% had sleep-related disorder. In this cohort, 2% of the patients did not perform all of the evaluation at our center and were reported as having missing data. The reasons for referral are presented in Fig. 1. The majority of patients were referred for the evaluation of dyspnea (51%) or chest pain (31%). Overall, abnormal CPET was observed in 77% of patients who had normal MPI and in 88% of patients with abnormal MPI ($P = .007$).

Patients with Normal MPI

Of the 415 patients in the study, 269 (65%) had normal MPI. Of these patients, 206 (77%) had abnormal CPET. Baseline demographic characteristics were similar in patients with and without CPET abnormalities. Compared to patients with normal CPET and normal MPI, patients with abnormal CPET but normal MPI had higher BMI (30 ± 6 vs 28 ± 4 kg/m^2, $P < .01$). There was a trend for higher proportion of chest pain and dyspnea as the presentation in patients with normal MPI/abnormal CPET, although the difference was not statistically significant (Table 1). In addition, patients with normal MPI but abnormal CPET demonstrated abnormal blood pressure response ($P < .01$) and heart rate response during stress testing ($P = .01$) more frequently (Table 2). Abnormal CPET was also associated with decreased exercise time (6.9 ± 1.9 vs 9.8 ± 2.6 min, $P < .01$), decreased functional aerobic capacity (78 ± 16% vs 105 ± 19%, $P < .01$), and decreased metabolic equivalents (METS) (7.0 ± 2.0 vs 9.5 ± 2.6, $P < .01$) (Table 2).

In patients with normal MPI, an abnormal pulmonary response on CPET was associated with an increased referral to Pulmonary Medicine (37.2% vs 4.0%, $P < .001$). Decreased VO_2 resulted in management of deconditioning more frequently compared to normal VO_2 (35.4 vs 18.2, $P = .004$). In patients where CPET showed cardiac output limitation, medication therapy was augmented in 20.0% vs 8.1% of cases in which CPET showed no cardiac limitation ($P = .006$). Referral for coronary angiography was not significantly different between people with abnormal and normal CPET (5.8% vs 3.2%, $P = .34$). Among the 13 (5.8%) patients who were referred for coronary angiography in the abnormal CPET group, PCI was performed in 2 patients with two-vessel disease for lesions both <70%. The remaining of the patients who were referred for cardiac catheterization did not undergo revascularization. One patient was directly referred for CABG after MPI/CPET (based on results of prior recent cardiac catheterization that revealed triple-vessel disease >70%).

Patients with Abnormal MPI

Of the 415 patients in the study, 146 (35%) had abnormal MPI. Of these patients, 128 (88%) had abnormal CPET. Patients with abnormal CPET, compared to patients with normal CPET, had higher BMI (31 ± 11 vs 28 ± 4 kg/m^2, $P = .01$) and a higher prevalence of systolic dysfunction (defined as LVEF <50%) (44% vs 17%, $P < .01$). Chest pain was the presentation in 31% of patients with normal MPI and 30% of patients with abnormal MPI. In addition, patients with abnormal CPET were more likely to have a history of valvular heart disease compared to patients with normal CPET (23% vs 0%, $P = .02$) (Table 1). In

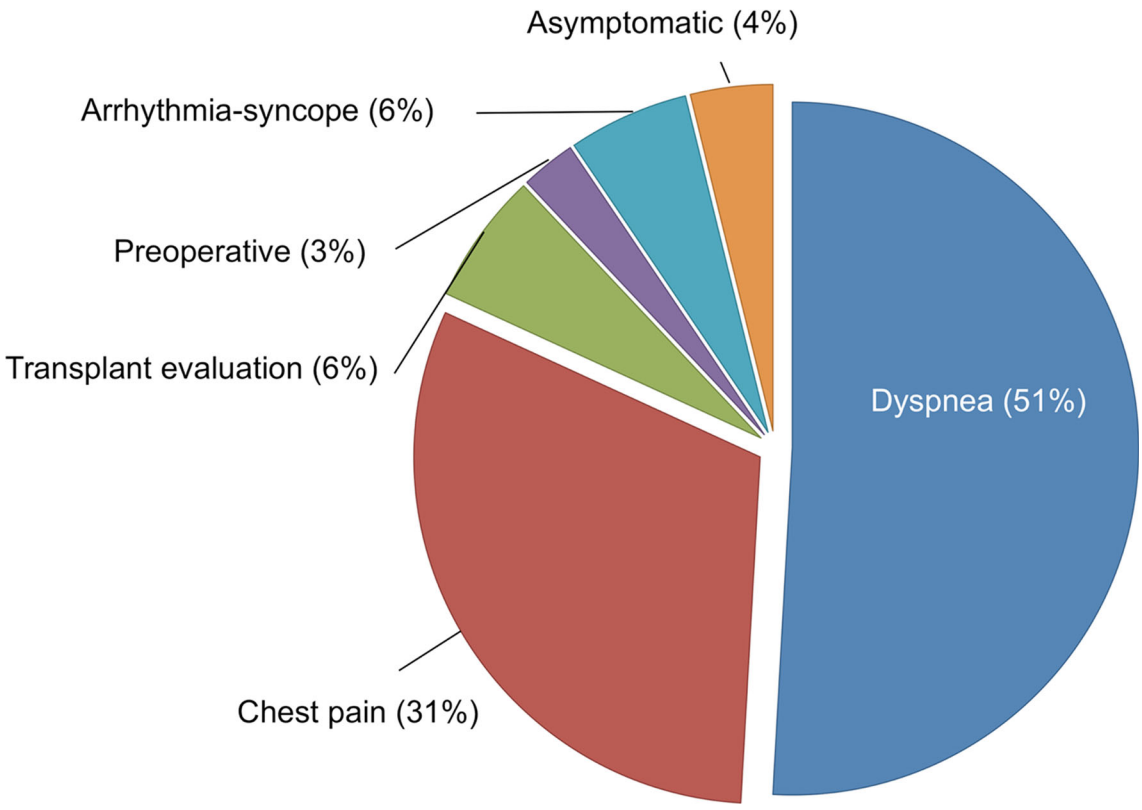

Figure 1. Reasons for referral for combined SPECT MPI and CPET.

regards to stress-testing data, post-stress wall motion abnormalities (independent of LVEF) were noted more frequently in patients with CPET abnormalities (5 [3-13] vs 2 [1-8] segments, $P = .04$) and those patients also demonstrated abnormal blood pressure responses ($P < .01$) and heart rate responses ($P = .01$) more frequently. Finally, patients with CPET abnormalities, as compared to patients without CPET abnormalities, had significant differences in exercise time, functional aerobic capacity, and metabolic equivalents ($P < .01$, Table 2).

In patients with abnormal MPI and abnormal CPET, most of the clinical decision-making was directed toward treatment of myocardial ischemia. In patients with a cardiac limitation on CPET, referral for cardiac catheterization was observed more frequently compared to patients with a normal cardiac response (33.3% vs 14.7%, $P = .009$). Of note, this increased referral rate was not influenced by discrepancies in the presence of reversible defects on MPI between patients with or without cardiac impairment (20/26 patients [77%] vs 7/10 [70%], $P = .99$). In addition, patients with reversible defects (compared to patients with non-reversible defects) on MPI did not have a statistically increased rate of referral to cardiac catheterization (29% vs 17%, $P = .10$). Cardiac impairment on CPET was associated with an increased referral rate in patients with reversible defects (20% vs 7%, $P = .02$), but not in patients with fixed defects (22% vs 12%, $P = .47$). Patients without cardiac limitation received counseling for deconditioning more frequently compared to patients with cardiac limitation (32.4% vs 14.1%, $P = .009$). Medication changes and management of pulmonary issues did not significantly differ in patients with abnormal vs patients with normal CPET when the MPI was also abnormal (Table 4).

The Role of Left Ventricular Ejection Fraction Calculated by MPI on Downstream Evaluation

LVEF was calculated by MPI in 389 patients, whereas in 26 patients it was indeterminate, and was found to be <50% in 91 of the 389 patients. If LVEF <50% was used to define an abnormal perfusion imaging study (regardless of perfusion defects), CPET addition had similar impacts on downstream evaluation and treatment. Specifically, of the 415 patients in the study, 238 patients had normal MPI (based on perfusion

Table 1. Patient demographics

Variable	Normal perfusion (n = 269)			Perfusion defect (n = 146)		
	Abnormal cardiopulmonary testing (n = 206)	Normal cardiopulmonary testing (n = 63)	P	Abnormal cardiopulmonary testing (n = 128)	Normal cardiopulmonary testing (n = 18)	P
Age (years)	63 ± 12	64 ± 12	NS	65 ± 12	67 ± 10	NS
Male (%)	57	63	NS	77	67	NS
Body mass index (kg/m^2)	30 ± 6	28 ± 4	<0.01	31 ± 11	28 ± 4	0.01
Hypertension (%)	61	46	0.04	64	83	NS
Hyperlipidemia (%)	60	63	NS	73	94	NS
Diabetes mellitus (%)	16	11	NS	28	28	NS
Smoking (%)						
Current	3	0	NS	6	6	NS
Past	51	43	NS	40	35	NS
Never	46	57	NS	54	59	NS
Presentation (%)						
Chest pain	31	25	NS	30	50	0.05
Dyspnea	53	46	NS	52	28	NS
Arrhythmia/ syncope	3	15	<0.01	5	6	NS
Heart transplant evaluation	9	8	NS	1	0	NS
Pre-operative	2	0	NS	6	0	NS
Asymptomatic	2	7	0.05	5	16	NS
Prior CAD (%)						
Yes-single vessel	15	14	NS	22	28	NS
Yes-two vessels	5	5		6	11	
Yes-three vessels	16	11		48	28	
Prior myocardial infarction (%)	10	3	NS	36	28	NS
Prior PCI (%)	20	13	NS	46	50	NS
Prior CABG (%)	8	5	NS	33	28	NS

Table 1. continued

Variable	Normal perfusion (n = 269)			Perfusion defect (n = 146)		
	Abnormal cardiopulmonary testing (n = 206)	Normal cardiopulmonary testing (n = 63)	P	Abnormal cardiopulmonary testing (n = 128)	Normal cardiopulmonary testing (n = 18)	P
CHF (%)						
Yes-LVEF <50%	12	7	NS	44	17	0.02
Yes-LVEF ≥50%	10	7		7	0	
Valvular heart disease (%)	12	6	NS	23	0	0.02
Atrial fibrillation/ flutter (%)	19	13	NS	18	6	NS
Ventricular arrhythmia (%)	6	10	NS	7	11	NS
Cerebrovascular disease (%)	5	3	NS	4	0	NS
COPD (%)	4	3	NS	9	6	NS
Sleep disorder (%)	18	18	NS	22	17	NS
Medications (%)						
B-blocker	48	33	0.04	73	61	NS
Calcium-channel blocker	20	14	NS	9	28	0.02
ACE inhibitor	24	16	NS	32	50	NS
Angiotensin receptor inhibitor	17	17	NS	18	17	NS
Aldosterone antagonist	4	0	NS	6	6	NS
Diuretic	24	20	NS	29	42	NS
Long-acting nitrate	6	3	NS	17	17	NS
Ranolazine	1	2	NS	3	6	NS
Digoxin	3	0	NS	8	0	NS

Continuous variables are expressed as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables are expressed as percentages
ACE, angiotensin converting enzyme; *CABG*, coronary artery bypass grafting; *CAD*, coronary artery disease; *CHF*, congestive heart failure; *COPD*, chronic obstructive pulmonary disease; *LVEF*, left ventricular ejection fraction; *NS*, not significant; *PCI*, percutaneous coronary intervention

Table 2. Procedural characteristics

Variable	Normal perfusion (n = 269)			Perfusion defect (n = 146)		
	Abnormal cardiopulmonary testing (n = 206)	Normal cardiopulmonary testing (n = 63)	P	Abnormal cardiopulmonary testing (n = 128)	Normal cardiopulmonary testing (n = 18)	P
Mode of exercise (%)						
Treadmill	99	100	NS	99	89	0.04
Bike	1	0		1	11	
LVEF by perfusion	61 ± 11	61 ± 11	NS	48 ± 16	57 ± 11	0.01
Rest RWMA[a]	0	0	NS	3 (1-10)	1.5 (0-5)	NS
Stress RWMA[a]	0	0	NS	5 (3-13)	2 (1-8)	0.04
Δ (stress RWMA − rest RWMA) present (%)	0	0	NS	63	67	NS
ECG interpretation (%)						
Positive for ischemia	5	8	NS	7	6	0.05
Negative for ischemia	77	83		54	83	
Non-diagnostic	18	9		39	11	
Ischemia (stress defect) (%)	0	0	NS	63	67	NS
Infarction (fixed defect) (%)	0	0	NS	82	61	NS
Enlarged LV size (%)	10	11	NS	43	39	NS
Submaximal effort (%)	12	6	NS	18	17	NS
BP response to exercise (%)						
Normal	71	87	0.01	59	94	<0.01
Hypertensive	2	2	NS	2	0	NS
Hypotensive	4	2	NS	5	0	NS
Blunted—due to medication	10	3	NS	14	6	NS
Blunted—not due to medication	13	6	NS	19	0	NS

Table 2. continued

Variable	Normal perfusion (n = 269)			Perfusion defect (n = 146)		
	Abnormal cardiopulmonary testing (n = 206)	Normal cardiopulmonary testing (n = 63)	P	Abnormal cardiopulmonary testing (n = 128)	Normal cardiopulmonary testing (n = 18)	P
Abnormal HR response (%)	51	33	0.02	67	33	0.01
Abnormal heart rate recovery (%)	52	32	0.01	55	22	0.01
Limited peak VO_2 (%)	88	0	<0.01	94	0	<0.01
Cardiac output impairment (%)	46	0	<0.01	61	0	<0.01
Pulmonary impairment (%)	21	0	<0.01	25	0	<0.01
Exercise time (min)	6.9 ± 1.9	9.8 ± 2.6	<0.01	6.5 ± 2.0	8.8 ± 2.8	<0.01
FAC	78 ± 16	105 ± 19	<0.01	70 ± 18	102 ± 18	<0.01
METS	7.0 ± 2.0	9.5 ± 2.6	<0.01	6.3 ± 2.3	9.2 ± 2.9	<0.01
Peak VO_2 (mL/kg/min)	19 ± 5	27 ± 7	<0.01	17 ± 6	26 ± 8	<0.01
RER	1.16 ± 0.12	1.15 ± 0.08	NS	1.13 ± 0.10	1.12 ± 0.14	NS
VCO_2/RER nadir	30 ± 5	27 ± 3	<0.01	31 ± 6	29 ± 3	<0.01

Continuous variables are expressed as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables are expressed as percentages

[a] Represents sum of points for each of 17 myocardial segments, as follows: 0, normal perfusion; 1, mild perfusion defect; 2, moderate perfusion defect; 3, severe perfusion defect; 4, absent perfusion

BP, blood pressure; *ECG*, electrocardiogram; *FAC*, fractional aerobic capacity; *HR*, heart rate; *LV*, left ventricle; *LVEF*, left ventricular ejection fracture; *METS*, metabolic equivalents; *NS*, not significant; *RER*, respiratory exchange ratio; *RWMA*, regional wall motion abnormalities; *VCO_2*, CO_2 consumption; *VO_2*, O_2 consumption

Table 3. Clinical outcomes based on CPET abnormality in patients with normal MPI ($n = 269$)

	Abnormal CPET ($n = 206$)	Normal CPET ($n = 63$)	*P*	Pulmonary impairment ($n = 43$)	No pulmonary impairment ($n = 226$)	*P*	Cardiac output impairment ($n = 95$)	No cardiac output impairment ($n = 174$)	*P*	Decreased VO_2 ($n = 181$)	Normal VO_2 ($n = 88$)	*P*
Pulmonary issues addressed, *n* (%)	24 (11.7)	2 (3.2)	0.04	17 (39.5)	9 (4.0)	<0.001	12 (12.6)	14 (8.1)	NS	17 (9.4)	9 (10.2)	NS
Inhaler	2 (0.9)	0 (0)	NS	2 (4.6)	0 (0.0)	0.03	1 (1.1)	1 (0.6)	NS	1 (0.6)	1 (1.1)	NS
Referral to pulmonary medicine	24 (11.7)	1 (1.6)	0.02	16 (37.2)	9 (4.0)	<0.001	12 (12.6)	13 (7.5)	NS	18 (9.9)	7 (7.9)	NS
Pulmonary function tests	3 (1.5)	1 (1.6)	NS	3 (7.0)	1 (0.4)	0.01	2 (2.1)	2 (1.2)	NS	1 (0.6)	3 (3.4)	NS
Deconditioning addressed, *n* (%)	69 (33.5)	11 (17.4)	0.01	9 (20.9)	71 (31.4)	NS	31 (32.6)	49 (28.2)	NS	64 (35.4)	16 (18.2)	0.004
Weight loss	26 (12.6)	5 (7.9)	NS	3 (7.0)	28 (12.4)	NS	12 (12.6)	19 (10.2)	NS	25 (13.8)	6 (6.8)	NS
Exercise counseling	38 (18.4)	7 (11.1)	NS	4 (9.3)	41 (18.1)	NS	16 (16.8)	29 (16.7)	NS	34 (18.8)	11 (12.5)	NS
Exercise prescription/ referral to cardiac rehabilitation	22 (10.7)	2 (3.2)	NS	1 (2.3)	23 (10.2)	NS	11 (11.6)	13 (7.4)	NS	21 (11.6)	3 (3.4)	0.04
Referral for catheterization	13 (5.8)	2 (3.2)	NS	2 (4.6)	13 (5.8)	NS	6 (6.3)	9 (5.2)	NS	11 (6.1)	4 (4.6)	NS
Revascularization, PCI	2 (0.9)	0 (0)	NS	1 (2.3)	1 (0.4)	NS	1 (1.1)	1 (0.6)	NS	0 (0.0)	2 (2.3)	NS
Revascularization, CABG	1 (0.5)	0 (0)	NS	0 (0.0)	1 (0.4)	NS	0 (0.0)	1 (0.6)	NS	1 (0.6)	0 (0.0)	NS
Heart failure medication changes, *n* (%)	39 (18.9)	9 (14.3)	NS	12 (27.9)	36 (15.9)	NS	26 (27.3)	22 (12.6)	0.003	34 (18.8)	14 (15.9)	NS
Add/increase dose	27 (13.1)	6 (9.5)	NS	8 (18.6)	25 (11.1)	NS	19 (20.0)	14 (8.1)	0.006	23 (12.7)	10 (11.4)	NS
Remove/decrease dose	14 (6.8)	3 (4.8)	NS	5 (11.6)	12 (5.3)	NS	8 (8.4)	9 (5.2)	NS	13 (7.2)	4 (4.6)	NS

Table 3. continued

	Abnormal CPET ($n = 206$)	Normal CPET ($n = 63$)	P	Pulmonary impairment ($n = 43$)	No pulmonary impairment ($n = 226$)	P	Cardiac output impairment ($n = 95$)	No cardiac output impairment ($n = 174$)	P	Decreased VO_2 ($n = 181$)	Normal VO_2 ($n = 88$)	P
Referral for ICD/CRT upgrade, *n* (%)	1 (0.5)	0 (0)	NS	0 (0.0)	1 (0.4)	NS	1 (1.1)	0 (0.0)	NS	1 (0.6)	0 (0.0)	NS
Missing data, *n* (%)	3 (1.5)	2 (3.2)	NS	0 (0.0)	5 (2.2)	NS	2 (2.1)	3 (1.7)	NS	3 (1.7)	2 (2.3)	NS

CABG, coronary artery bypass grafting; *CAD*, coronary artery disease; *CPET*, cardiopulmonary exercise testing; *CRT*, cardiac resynchronization therapy; *ICD*, implantable cardioverter-defibrillator; *MPI*, myocardial perfusion imaging; *NS*, not significant; *PCI*, percutaneous coronary intervention

only) and LVEF >50% (or indeterminate LVEF) and 177 patients had abnormal MPI or LVEF <50%.

In the first group (both no perfusion abnormality and LVEF >50%), an abnormal CPET would lead to changes in evaluation and management similar to as described in Table 3. In this group, patients had management of pulmonary disease more frequently if they had evidence of pulmonary impairment vs no evidence of pulmonary impairment on CPET (13 patients [38%] vs 8 patients [4%], $P < .001$). They also had more frequent medication changes if their CPET showed cardiac limitation vs it did not show cardiac limitation (18 patients [23%] vs 18 patients [11%], $P = .02$). Finally, they were more frequently managed for deconditioning if they had low VO_2 vs if they had normal VO_2 (56 patients [35%] vs 15 patients [19%], $P = .01$).

In the second group (either perfusion defects present or LVEF <50%), an abnormal CPET did not significantly determine downstream evaluation and management; similar to what was seen in patients with perfusion defects only (Table 4). The one exception was that pulmonary impairment on CPET led to significantly increased rate of pulmonary disease management compared to no pulmonary impairment (7 patients [17%] vs 3 patients [2%], $P < .001$). Otherwise, medication changes, cardiac catheterization rates, and management of deconditioning did not significant change based on CPET variables.

Multivariable Analysis in the Whole Population

On multivariable analysis, the presence of pulmonary impairment of CPET was associated with a 10-fold increase in management of pulmonary disease (OR 10.1, 95% CI 4.3-24.4, $P < .001$), whereas stress-induced ischemia on MPI led to significant decrease of management of pulmonary disease (OR 0.1, 95% CI 0.02-0.4, $P = .007$). Management of deconditioning was most strongly associated with BMI >30 (OR 2.9, 95% CI 1.7-4.9, $P < .001$, female sex (OR 1.8, 95% CI 1.1-3.0, $P = .02$) and dyspnea on presentation (OR 2.0, 95% CI 1.2-3.3, $P = .006$). Referral for cardiac catheterization was driven by chest pain (OR 2.3, 95% CI 1.1-4.8, $P = .02$) and reversible defects on MPI (OR 3.4, 95% CI 1.7-6.8, $P < .001$). Finally, changes in heart failure medications were associated with dyspnea on presentation (OR 2.4, 95% CI 1.5-4.0, $P < .001$) and low VO_2 on CPET (OR 2.2, 95% CI 1.3-4.0, $P = .006$) (Supplemental Table 1).

DISCUSSION

Our study demonstrated that (1) CPET abnormalities were found in a substantial portion of the patients

Table 4. Clinical outcomes based on CPET abnormality in patients with abnormal MPI ($n = 146$)

	Abnormal CPET ($n = 128$)	Normal CPET ($n = 18$)	*P*	Pulmonary impairment ($n = 33$)	No pulmonary impairment ($n = 113$)	*P*	Cardiac output impairment ($n = 78$)	No cardiac output impairment ($n = 68$)	*P*	Decreased VO_2 ($n = 120$)	Normal VO_2 ($n = 26$)	*P*
Pulmonary issues addressed, *n* (%)	5 (3.9)	0 (0)	NS	3 (9.1)	2 (1.8)	NS	3 (3.9)	2 (2.9)	NS	5 (4.2)	0 (0.0)	NS
Inhaler	1 (0.8)	0 (0)	NS	1 (3.0)	0 (0.0)	NS	0 (0.0)	1 (1.5)	NS	1 (0.8)	0 (0.0)	NS
Referral to pulmonary medicine	4 (3.1)	0 (0)	NS	2 (6.1)	2 (1.8)	NS	3 (3.9)	1 (1.5)	NS	4 (3.3)	0 (0.0)	NS
Pulmonary function tests	0 (0)	0 (0)	NS	0 (0.0)	0 (0.0)	NS	0 (0.0)	0 (0.0)	NS	0 (0.0)	0 (0.0)	NS
Deconditioning addressed, *n* (%)	28 (21.9)	5 (27.8)	NS	6 (18.2)	27 (23.9)	NS	11 (14.1)	22 (32.4)	0.009	28 (23.3)	5 (19.2)	NS
Weight loss	8 (6.2)	2 (11.1)	NS	2 (6.1)	8 (7.1)	NS	4 (5.1)	6 (8.8)	NS	8 (6.7)	2 (7.7)	NS
Exercise counseling	15 (11.7)	2 (11.1)	NS	2 (6.1)	15 (13.3)	NS	2 (2.6)	15 (22.1)	<0.001	15 (12.5)	2 (7.7)	NS
Exercise prescription/ referral to cardiac rehabilitation	11 (8.6)	2 (11.1)	NS	4 (12.1)	9 (8.0)	NS	7 (9.0)	6 (8.8)	NS	11 (9.2)	2 (7.7)	NS
Referral for catheterization	34 (26.6)	2 (11.1)	NS	8 (24.2)	28 (24.9)	NS	26 (33.3)	10 (14.7)	0.009	32 (26.7)	4 (15.4)	NS
Revascularization, PCI	11 (8.6)	1 (5.6)	NS	3 (0.9)	9 (8.0)	NS	9 (11.5)	3 (4.4)	NS	9 (7.5)	3 (11.5)	NS
Revascularization, CABG	3 (2.3)	0 (0)	NS	1 (3.0)	2 (1.8)	NS	3 (3.9)	0 (0.0)	NS	3 (2.5)	0 (0.0)	NS
Heart failure medication changes, *n* (%)	42 (32.8)	4 (22.2)	NS	10 (30.3)	36 (31.9)	NS	22 (28.2)	24 (35.3)	NS	41 (34.2)	5 (19.2)	NS
Add/increase dose	37 (28.9)	4 (22.2)	NS	9 (27.3)	32 (38.3)	NS	20 (25.6)	21 (30.9)	NS	36 (30.0)	5 (19.2)	NS
Remove/decrease dose	8 (6.3)	0 (0.0)	NS	2 (6.1)	6 (5.3)	NS	5 (6.4)	3 (4.4)	NS	7 (5.8)	1 (3.9)	NS
Referral for ICD/CRT upgrade, *n* (%)	4 (3.1)	0 (0)	NS	1 (3.0)	3 (2.7)	NS	4 (5.1)	0 (0.0)	NS	4 (3.3)	0 (0.0)	NS
Missing data, *n* (%)	3 (2.3)	0 (0)	NS	2 (6.1)	1 (0.9)	NS	2 (2.6)	1 (1.5)	NS	3 (2.5)	0 (0.0)	NS

CABG, coronary artery bypass grafting; *CAD*, coronary artery disease; *CPET*, cardiopulmonary exercise testing; *CRT*, cardiac resynchronization therapy; *ICD*, implantable cardioverter-defibrillator; *MPI*, myocardial perfusion imaging; *NS*, not significant; *PCI*, percutaneous coronary intervention

with normal MPI (77%) and abnormal MPI (88%) ($P = .007$), (2) normal MPI/pulmonary impairment results in more frequent downstream evaluation of pulmonary disease, (3) normal MPI/cardiac output impairment leads to advancement of medical therapy for heart failure, and (4) normal MPI/decreased VO_2 leads to treatment of deconditioning. To our knowledge, this is the first study to examine a combined CPET/SPECT MPI protocol.

A powerful characteristic of CPET is its ability to distinguish between cardiac and pulmonary disease.[20–25] Several CPET abnormalities, such as the VE/VCO_2, $P_{ET}CO_2$, oxygen uptake efficiency slope, and breathing reserve can be used for that differentiation. Our study specifically used low rise in VO_2 max, a RER <1.15, a BR <10%, and a high VE/VCO_2, among others. Based on those parameters, 24 (11.7%) patients with normal MPI/abnormal CPET had management of pulmonary issues, compared to only 2 (3.2%) of patients with normal MPI/normal CPET ($P = .04$, patients needed to test = 11.8). In addition, only patients with normal MPI seemed to be treated for pulmonary issues more frequently. Importantly, addition of CPET to MPI may be considered for the patient that present primarily with dyspnea, rather than chest pain.

Identification and management of patients with deconditioning is perhaps the most common contribution of combined MPI and CPET. This occurred to 33.5% of patients with normal MPI/abnormal CPET, compared to only 17.4% of patients with normal MPI/normal CPET ($P = .01$, number needed to test = 6.2). Decrease in VO_2 was shown to correlate best with this change, which is consistent with the literature.[26] Additional parameters that can be used to determine the need and intensity of exercise prescriptions include VO_2 reserve (difference between resting and peak VO_2) and heart rate reserve (difference between basal and peak heart rate).[26–28]

Currently, the use of CPET as a diagnostic tool to detect coronary ischemia is not endorsed in the 2012 and 2016 Joint Statements of the European Association for Cardiovascular Prevention and Rehabilitation and the American Heart Association,[20,29] particularly since only limited studies suggest that CPET may be of value in such an evaluation.[30–33] However, it is possible that in patients with abnormal MPI, the additional finding of abnormal CPET (such as cardiac impairment) may assist in the work-up for cardiac ischemia by indicating increased CAD severity and thus expedite coronary angiography. Our study did not demonstrate a significant increase in referral rates for coronary catheterization or CAD revascularization in patients with abnormal CPET and normal or abnormal MPI (compared to the patients with normal CPET). Of note, the patients with abnormal CPET/normal MPI who did undergo PCI after being referred for cardiac catheterization had both stents placed in <70% lesions.

Determining who may benefit from CPET as well as timing of combined or sequential MPI/CPET testing may be challenging. Since CPET is an expensive diagnostic tool with more limited availability, it is important to specify the patient populations that would benefit from its addition to the standard work-up of chest pain or dyspnea. Limitations to CPET use include higher cost than testing without CPET (i.e., exercise ECG without CPET or SPECT MPI without CPET), technical difficulties associated with calibration, and more limited expertise in performing and interpreting the test. Addition of CPET to stress testing should be directed to specific patient groups where combined testing may have a higher diagnostic yield. Our study demonstrated a benefit of CPET mostly when the MPI is normal (Tables 3, 4). This finding suggests that it may be more cost-efficient to perform MPI studies first and add CPET if the former is normal. Concurrent testing may be advisable if cost is not a limiting factor and in special populations in which CAD is not the most suspected diagnosis but needs to be ruled out in the presence (or even absence) of CAD-risk factors. Such populations may include younger females, patients with advanced lung disease, patients with prior normal coronary angiograms, and patients with congestive heart failure likely from non-ischemic cardiomyopathy.

Several important limitations merit discussion: (1) the current analysis does not serve to assess the diagnostic accuracy of CPET for CAD or other cardiopulmonary conditions, and rather it sought to evaluate its impact on clinical decision-making; (2) downstream evaluation of patients may have been affected by reasons that are unrelated to results of CPET, including patient preference or strong clinical suspicion; (3) the observational study design introduces selection bias since referral for combined testing is more likely to occur when other cardiac or pulmonary conditions other than coronary artery disease are suspected; (4) the study was performed at a single tertiary center thus limiting its generalizability to other medical centers where CPET is not readily available and a multidisciplinary approach is less feasible; (5) the study may have been underpowered to detect significant differences in regards to cardiac catheterization and medication changes, among others, as suspected by the trend seen in those categories; and (6) the study did not describe long-term outcomes in patients who were tested.

In conclusion, in an observational tertiary referral center study, CPET is commonly abnormal in patients with normal perfusion imaging and is associated with increased referral rates to pulmonary medicine and management of deconditioning factors. When perfusion

imaging is abnormal, CPET is also commonly abnormal but management of these issues is less frequent. Combined testing should be considered in patients where ischemia is not the most likely diagnosis, but needs to be ruled out.

NEW KNOWLEDGE GAINED

Over three-quarters of patients undergoing combined CPET-MPI imaging have a normal perfusion study but an abnormal CPET assessment. These patients are more likely to undergo further assessment and management of pulmonary conditions and deconditioning when compared to patients who had both normal MPI and CPET. Therefore, the addition of CPET testing to MPI may be beneficial in diagnosing etiologies other than ischemia, such as pulmonary disorders and deconditioning, which could be contributing to the patient's symptomatology. Combined CPET-MPI testing should be considered when ischemia is being included as a component of the differential diagnosis but other etiologies are thought to be contributing to the patient's presentation.

Disclosure

All authors declare that they have no conflict of interest.

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