Diagnostic Yield of Customized Exercise Provocation Following Routine Testing

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Clinical guidelines advocate for customization of exercise testing to address patient-specific diagnostic goals, including reproduction of presenting exertional symptoms. However, the diagnostic yield of adding customized exercise testing to graded exercise in patients presenting with exertional complaints has not been rigorously examined and is the focus of this study. Using prospectively collected data, we analyzed the diagnostic yield of customized additional exercise provocation following inconclusive graded exercise test with measurement of gas exchange. Additional testing was defined as "positive" if it revealed a clinically-actionable diagnosis related to the chief complaint or reproduced symptoms in the absence of an explanatory diagnosis or pathology. Of 1,110 patients who completed a graded test, 122 (11%) symptomatic patients underwent additional customized exercise testing (e.g., sprint intervals and race simulations). Compared with those who did not undergo additional testing, this group was younger (29 [interquartile range 19 to 45] vs 46 [25 to 58] year old) and disproportionately female (43% vs 27%). Presenting symptoms included palpitations (46%), lightheadedness/syncope (25%), chest pain (14%), dyspnea (11%), and exertional intolerance (3%). Additional testing was "positive" in 48 of 122 (39%) of patients by revealing a clinically actionable diagnosis in 26 of 48 (54%) or reproducing symptoms without an explanatory diagnosis in 22 of 48 (46%). In conclusion, while patient-centered customization of exercise testing is suggested by clinical guidelines, these data are the first to demonstrate that the selective addition of customized exercise provocation following inconclusive graded exercise testing improves the diagnostic yield of exercise assessment. **(Am J Cardiol 2019;123:2044−2050)**

Exercise testing plays a crucial role in the diagnosis and management of cardiovascular disease.[1−3], and clinical guidelines emphasize that "exercise protocols should be individualized according to the type of subject being tested" and "according to the purposes of testing."[1,4−6] However, most clinical exercise labs default to a single graded-intensity protocol featuring large increments in work, most often the Bruce protocol,[7,8] which commonly do not replicate the physiologic conditions under which patients experience symptoms in the real world.[9,10] This approach may therefore fail to accomplish one of the primary goals of testing—the reproduction of patients' presenting exertional symptoms.[9] We hypothesized that the addition of customized exercise provocation (e.g., high-intensity sprints or sport-specific race simulations) after an unrevealing maximal-effort graded exercise protocol would improve the overall diagnostic yield of the exercise testing process. To address this hypothesis, we analyzed prospectively-collected data from a single, high-volume clinical exercise laboratory with a goal of determining the incremental diagnostic yield of customized additional testing.

Methods

The Cardiovascular Performance Program at the Massachusetts General Hospital focuses on the clinical care of active individuals, with patients ranging from the recreationally active to elite athletes. When indicated, patients are referred to a single exercise-testing laboratory to assess for exercise-associated pathology. All such patients undergo a maximal-effort graded test with measurement of gas exchange, with the exercise protocol tailored to account for each patient's projected fitness and habitual exercise modality as detailed below. Customized additional testing is routinely implemented in patients presenting with exertional symptoms in whom diagnostic uncertainty remains after the initial graded test, with the goal of testing under different physiologic conditions (i.e., burst or sustained moderate-effort activity) that more closely replicate those that provoke their presenting symptoms.

Data were prospectively collected on all patients referred to the Cardiovascular Performance Program who underwent exercise testing from December 2011 through October 2017 to investigate exertional symptoms. We included patients with symptoms concerning for coronary

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heart disease (ex. chest pain, exertional dyspnea) as well as those with exertional symptoms suggestive of other cardiopulmonary diagnoses (ex. palpitations, syncope, lightheadedness, and exertional intolerance). For patients with more than one exercise test, only the first test was included in this analysis. This study was approved by the Massachusetts General Hospital Institutional Review Board (Boston, Massachusetts).

All patients first performed a maximal-effort graded exercise test with continuous measurement of gas exchange. This test began with a decision by the patient, referring physician, and exercise physiologist as to the appropriate exercise modality, with the goal of matching testing to patients' regular form of exercise. Options included treadmill (Woodway Pro 27, Woodway USA, Waukesha, Wisconsin), upright cycle ergometer (Sport Excalibur Bicycle Ergometer, Lode, Holland), or rowing ergometer (Concept2 PM4, Concept2, Morrisville, Vermont). Exercise protocols for the graded test were defined by the exercise physiologist in collaboration with the patient, with starting intensity selected based on estimation of the patient's fitness for targeted test duration of 10 to 12 minutes of graded exercise. All test protocols proceeded until exhaustion, the onset of limiting symptoms, or the development of a clinical contraindication to continued exercise.[11] Cycle tests consisted of 3 minutes of free-wheel cycling followed by continual increase in resistance (varying from 10 to 40 watts per minute) until test completion. Treadmill tests began with 10-minute warm-up at 1% grade, followed by progressive increase in incline at fixed speed (3.0 to 7.5 miles per hour) until exhaustion. Tests on the rowing ergometer consisted of six 2-minute stages at increasing intensities followed by 2 minutes of maximal effort.

Graded exercise tests were performed with real-time 12-lead electrocardiography (ECG) monitoring (Mortara Instrument X12+ wireless ECG transmitter, Milwaukee, Wisconsin). Blood pressures were measured using a manual sphygmomanometer before exercise, at 3-minute intervals during exercise, immediately after peak exercise, and at 3-minute intervals during recovery.[12] Gas exchange was measured on a breath-by-breath basis using a Hans Rudolph V2 Mask (Hans Rudolph, Inc, Shawnee, Kansas), a commercially available metabolic cart and gas exchange analyzer (Ultima CardiaO2; Medgraphics Diagnostics, St. Paul, Minnesota) and analyzed using Breeze Suite software (Medgraphics Diagnostics, Version 8.2, 2015). Oxygen saturation was monitored with a clinical pulse oximeter (Nonin 7500; Nonin Medical, Plymouth, Minnesota). Peak oxygen consumption ($\dot{V}O_2$) was defined as the highest oxygen uptake, averaged over a period of 30 seconds, during the last minute of symptom-limited exercise.[13] The peak respiratory exchange ratio (RER) was defined as exhaled carbon dioxide divided by oxygen consumption using the same 30-second average. Predicted $\dot{V}O_2$ was determined using the Jones equation.[14] Predicted heart rate was determined using 220 − age at time of testing. All tests included baseline spirometry; postexercise spirometry was also performed if there was clinical suspicion of respiratory pathology.

After completion of a maximal-effort graded test as described above, a subset of patients underwent additional exercise testing in the same session. Patients were considered for additional testing if they (1) presented with exertional symptoms suggestive of cardiovascular disease AND (2) completed a maximal-effort graded protocol that did not demonstrate explanatory pathology or succeed in reproducing presenting symptoms. The goal of additional exercise testing was to replicate the exercise conditions associated with their presenting symptoms to maximize the likelihood of detecting or excluding causal pathology. Additional testing protocols were determined in a collaborative fashion by the exercise physiologist and patient, with broad categories shown in Table 1. Monitoring used during additional testing (i.e., ECG, pulse oximetry, blood pressure, repeat pre-/post-spirometry) was individualized based on symptoms; gas exchange measurement was not used during additional testing.

Two cardiologists (T.C. and T.S.) separately reviewed medical records (exercise test report and associated clinic notes) for all patients undergoing additional testing to assess presenting symptom(s), results of initial graded exercise test, and results of additional exercise testing. Results of initial graded exercise test were classified as follows: (1) normal (normal testing parameters without symptom provocation), (2) normal with symptoms (normal testing with provocation of presenting symptoms), (3) inadequate effort (defined as a RER <1.0),[15] or (4) abnormal (defined as any abnormality in ECG tracing [arrhythmia, ischemia], heart rate or blood pressure response, oxygen saturation, or other gas exchange measurements). Specifically, myocardial ischemia was defined as 1 mm horizontal or downsloping ST-segment depression in 2 or more contiguous leads.[1,16] Abnormal blood pressure response to exercise was defined as peak systolic pressure over 210 mmHg in males or 190 mmHg in females[1] or a decline in systolic blood pressure during exercise. Chronotropic incompetence was defined as a peak HR <85% predicted despite adequate RER.

For patients presenting with exertional symptoms, we defined additional testing as "positive" if it either (1a) provided evidence of a clinically-actionable diagnosis that explained the patient's presenting complaint OR (1b) reproduced the patient's presenting symptoms in absence of

Table 1
Categories of additional testing

Category	Description
Sprints	High- or maximal-intensity efforts lasting 2 minutes or less in duration, alternating with short rest periods
Race simulation	Submaximal-effort exercise for a fixed distance or duration, typically consistent with a patient's sport-specific race effort
Steady state	Moderate intensity exercise (based on patients' subjective assessment of effort or ≤80% peak watts on cycle tests) lasting over 2 minutes in duration
Other	Other sport-specific exercise (i.e., boxing, plyometrics)

pathology, such that reassurance could be given; AND (2) these findings (1a or 1b) were not available from the initial graded exercise test. A clinically-actionable diagnosis was defined as either a pathologic abnormality during testing (i.e., arrhythmia) or an accentuation of normal physiology (ex. accelerated drop in blood pressure after exercise) that could be treated pharmacologically, procedurally, or with behavioral/lifestyle modification. Additional testing was considered to be "negative" if it failed to meet the above criteria. If the 2 reviewing cardiologists differed in their categorization of the results of initial graded testing or the outcome of additional testing according to definitions above, a third experienced cardiologist (M.W.), blinded to the initial categorization, adjudicated the results.

Normality of distribution for all variables was assessed using the Shapiro-Wilk test. Continuous variables are reported as mean ± standard deviation or median (interquartile range) based on data normality. Categorical variables are reported as number (percent). Baseline characteristics of patients who did and did not undergo additional testing were compared using 2-tailed unpaired *t* Tests or the Mann-Whitney test for continuous variables, and Fisher's exact test or the chi-squares test for categorical variables, as appropriate for data distribution. Data analysis was performed using STATA 12.1 (STATA Corporation, College Station, Texas).

Results

A total of 1,110 patients completed clinically-indicated exercise testing during the study period and were included in this analysis (Table 2). Male patients were older than females (48 [29 to 59] vs 33 [20 to 51] years old, p value <0.001). Most females completed initial maximal-effort graded testing on the treadmill (n = 181, 57%), while the majority of males did so on the cycle ergometer (n = 411, 52%; p value <0.001). Fitness level, as reflected by peak $\dot{V}O_2$, was supranormal at 120 ± 31% predicted.

A subset of 122 symptomatic patients (11%) performed additional customized exercise testing after completion of the maximal-effort graded exercise protocol (Table 2). Three illustrative cases of patients who underwent additional testing are presented in Figure 1. As compared with patients who did not undergo any additional testing, this group was younger and disproportionately female. The frequency of adequate initial testing (defined by RER ≥1) was similar between the 2 groups. Although the additional testing group had a higher peak $\dot{V}O_2$ and heart rate, these were similar when assessed relative to age-predicted values. The most common presenting symptom in the additional testing group was palpitations (n = 56/122 patients, 46%), followed by lightheadedness/syncope (n = 31/122, 25%), chest pain (n = 17/122, 14%), dyspnea (n = 14/122, 11%), and exertional intolerance (n = 4/122, 3%).

Most patients (90 of 122, 74%) who underwent additional testing had a normal initial graded exercise test that was completed without symptom provocation or testing abnormalities. In the remaining patients (32 of 122, 26%), abnormal findings on the initial graded exercise test were unrelated to the patient's chief complaint in 18 of 32 (56%) or were equivocal in nature in 8 of 32 (25%). In 6 of 32 patients (19%), symptoms were elicited but to a less severe degree than the presenting complaint.

Table 2
Demographics and initial graded exercise testing results

Variable	All patients (n = 1,110)	Inclusion of additional testing		p Value
		Additional testing completed (n = 122)	No additional testing completed (n = 988)	
Age (years)	44 [23−57]	29 [19−45]	46 [25−58]	<0.001
Men	795 (72%)	69 (57%)	726 (73%)	<0.001
Weight (pounds)	170 [148−191]	163 [137−176]	170 [150−193]	<0.001
Height (inches)	69 [67−72]	69 [66−71]	69 [67−72]	0.04
Body mass index (kg/m^2)	25 [23−27]	24 [22−26]	25 [23−27]	<0.001
Race				
White	1,026 (92%)	112 (92%)	914 (93%)	0.07
Black	39 (4%)	2 (2%)	37 (4%)	
Other	45 (4%)	8 (7%)	37 (4%)	
Initial graded exercise testing				
Exercise testing modality				
Treadmill	523 (47%)	76 (62%)	447 (45%)	<0.001
Cycle ergometer	521 (47%)	37 (30%)	484 (49%)	
Rowing ergometer	66 (6%)	9 (7%)	57 (6%)	
Peak oxygen consumption (ml/kg/min)	41 ± 12	45 ± 10	40 ± 13	<0.001
Peak oxygen consumption, % predicted	120 ± 31%	124% ± 24%	119% ± 32%	0.11
Peak respiratory exchange ratio	1.18 ± 11	1.19 ± 0.11	1.18 ± 0.11	0.48
Adequate test (respiratory exchange ratio ≥1)	1,077 (97%)	120 (98%)	957 (97%)	0.42
Peak heart rate (beats/ min)	174 [158−186]	182 [171−193]	172 [157−184]	<0.001
Peak heart rate, % predicted	97% [91−102%]	97% [92−101%]	97% [91−102%]	0.98

Values are reported as median [interquartile range] or mean ± standard deviation as appropriate for data distribution. Respiratory exchange ratio is defined as the ratio of exhaled carbon dioxide to oxygen consumption; values over 1.00 are considered adequate effort tests.

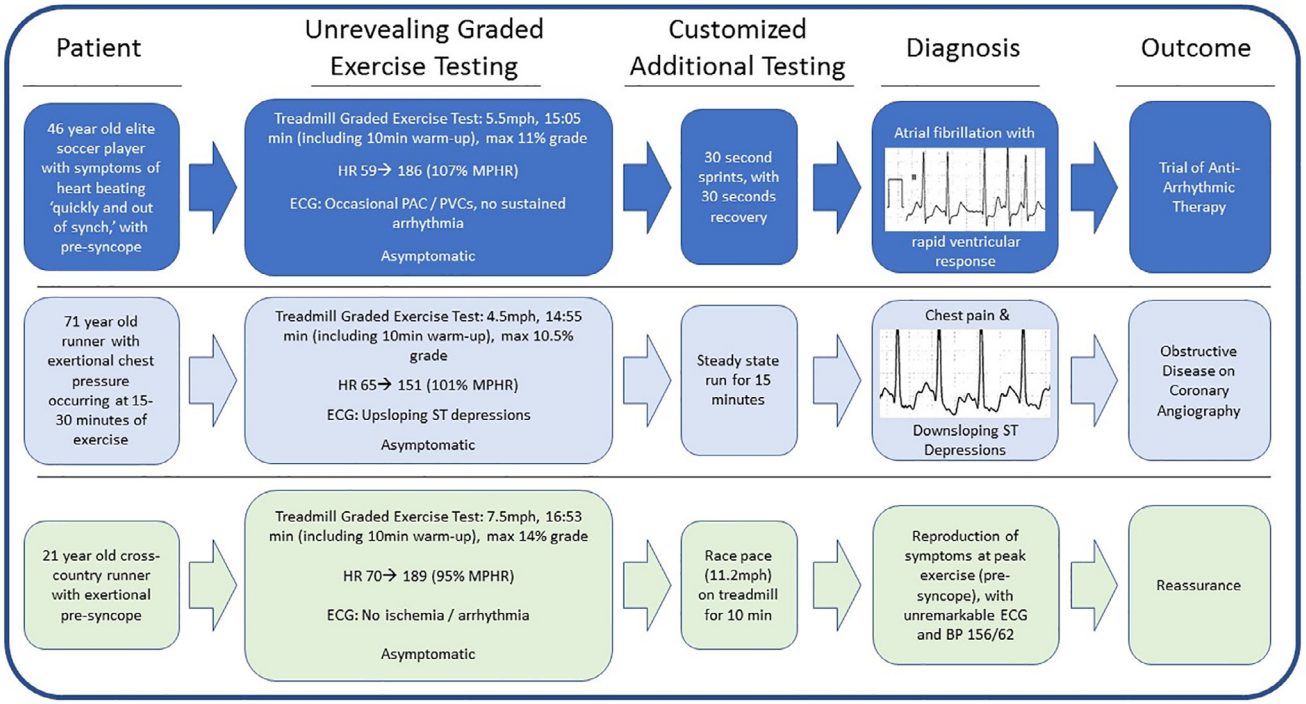

Figure 1. Illustrative examples of three cases of positive additional testing.
Three illustrative cases of patients who underwent customized additional exercise provocation after completion of an unrevealing graded-effort exercise protocol are shown. The additional testing revealed previously undiagnosed pathology in the first 2 cases, whereas in the third it succeeded in reproducing the patient's presenting exertional symptoms without testing abnormalities, allowing the treating physician to broadly reassure the patient as to the benign nature of her symptoms.

The distribution of types of additional exercise provocation and the corollary diagnostic yield are shown in Figure 2. The most common form of additional exercise provocation was sprint testing, which was completed by 86 of 122 (70%) patients, among whom 65 of 86 (76%) performed sprints on the treadmill, 14 of 86 (16%) on the cycle ergometer, and 7 of 86 (8%) on the rowing ergometer. Longer duration submaximal efforts (termed steady state) was the next most common type of additional testing (n = 27/122, 22%). Six patients (5%) completed a simulated race (ex. 5,000 meter run), and 3 (2%) performed other exercise off the usual testing apparatus, such as squat jumps or boxing simulation.

In symptomatic patients who completed additional customized exercise, the additional testing was "positive" in 39% (48 of 122). Of these, symptoms were linked to an explanatory and clinically actionable diagnosis in about half (Table 3). In the remaining patients, presenting symptoms were reproduced without any evidence of pathology. The rate of positive tests did not differ by gender. The diagnostic yield of sprint testing versus steady state exercise was similar, whereas all 6 race simulation tests were positive. Across all types of additional exercise provocation, the proportions of tests that reproduced symptoms linked to an actionable diagnosis versus those that reproduced symptoms without explanatory pathology were similar. Additional testing was most frequently positive in patients presenting with dyspnea or lightheadedness/syncope. Testing had lower yield but was still positive in a sizable number of patients presenting with chest pain or palpitations, whereas additional testing was not positive in any patient presenting with exertional intolerance.

Discussion

Using prospectively collected data from a tertiary-care referral center, we examined the diagnostic yield of customized exercise provocation following unrevealing maximal-effort graded exercise testing in patients presenting with symptoms suggestive of cardiovascular disease. Results from this study can be summarized as follows. Approximately 10 percent of patients referred for evaluation of exertional complaints had maximal-effort graded exercise tests that failed to accomplish the specific goals of testing and ultimately underwent additional customized exercise provocation to better replicate the physiologic conditions associated with their presenting symptoms. In this group, the addition of customized testing provided a diagnostic explanatory finding or reproduced symptoms in the absence of demonstrable cardiopulmonary pathology in more than 1 in 3 cases. Thus, these data indicate that the sequential use of a standardized maximal-effort graded protocol followed by patient-directed customized testing has the potential to increase the diagnostic yield of exercise testing in patients presenting with exertional symptoms.

Traditional graded exercise testing is most commonly performed to exclude or diagnose coronary artery disease and is well-validated to serve this specific goal,[1,17,18] with sensitivity and specificity reported at 68% and 77%, respectively.[19] Moving beyond this single diagnostic focus,

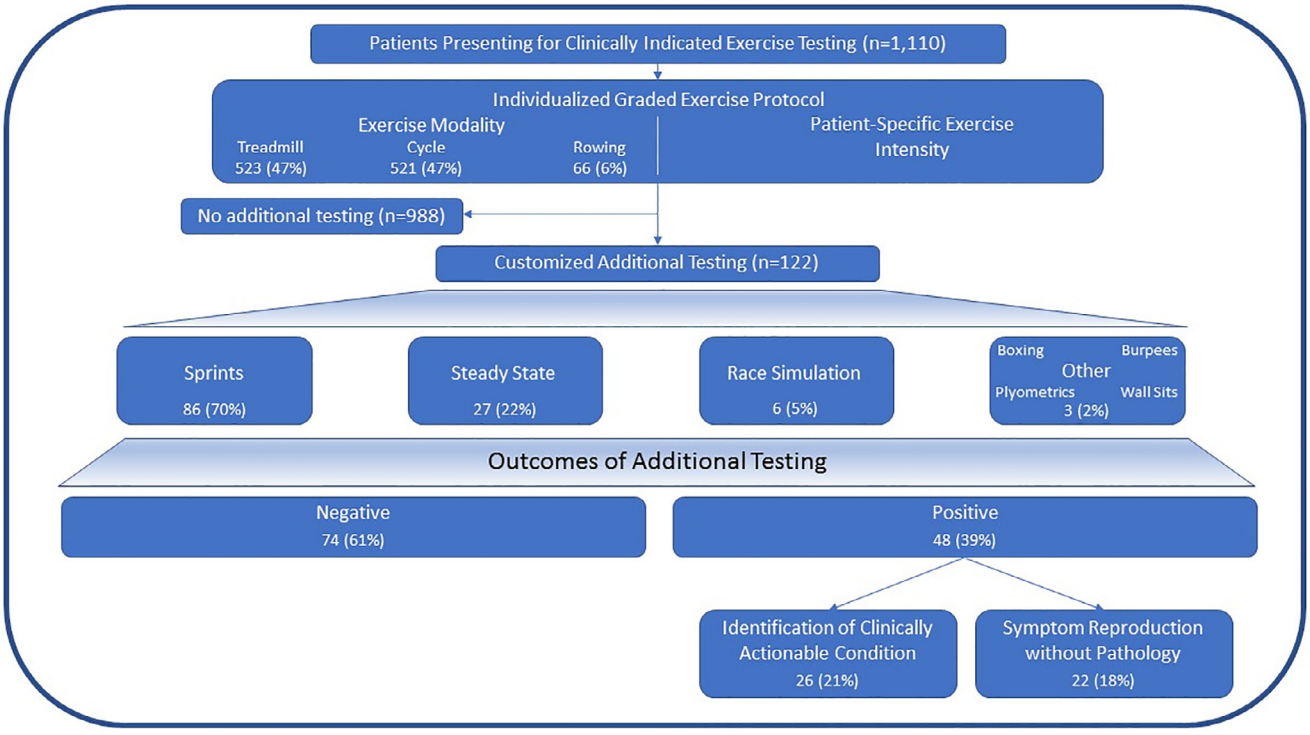

Figure 2. Diagnostic yield of customized additional exercise testing.
A total of 122 patients underwent customized additional testing after completion of a maximal-effort graded exercise test. Of these, the additional testing resulted in clinically meaningful information in 48 (39%), either by revealing discrete evidence of a clinically actionable condition or by eliciting the patient's symptoms in the setting of a normal test, thus allowing for clinical reassurance.

exercise testing has the potential to play a broader role in the diagnostic evaluation of patients, particularly those with undifferentiated exertional complaints. Specifically, laboratory-based exercise testing, particularly when customized for individual patients, is capable of identifying numerous cardiovascular abnormalities responsible for exertional symptoms including abnormal hemodynamic responses to exercise, chronotropic incompetence, and inducible arrhythmia. However, the diagnostic yield of customized exercise testing that is tailored to reproduced exertional symptoms has not previously been described.

The use of laboratory-based exercise testing to reproduce exertional symptoms is of paramount clinical importance in the evaluation of patients with exertional complaints. A "normal" exercise test that does not reproduce a patient's presenting symptoms is of minimal clinical

Table 3
Diagnostic yield of additional testing

			Positive tests	
	Negative	Positive	Identification of clinically actionable condition	Reproduction of symptoms without pathology
All additional testing	74 (61%)	48 (39%)	26	22
By gender				
Females	32 (60%)	21 (40%)	11	10
Males	42 (61%)	27 (39%)	15	12
By additional testing type				
Sprints	54 (63%)	32 (37%)	18	14
Steady state	18 (67%)	9 (33%)	4	5
Race simulation	0	6 (100%)	3	3
Other	2 (67%)	1 (33%)	1	0
By initial presenting symptom				
Palpitations	44 (79%)	12 (21%)	3	9
Lightheadedness/syncope	12 (39%)	19 (61%)	8	11
Dyspnea	4 (29%)	10 (71%)	7	3
Chest pain	10 (59%)	7 (41%)	4	3
Exertional intolerance	4 (100%)	0	0	0

value, particularly if the exercise provocation does not adequately replicate a patient's usual exercise routine,[6] and often leads to unnecessary downstream testing or underdiagnosis. By contrast, exercise testing that successfully reproduces symptoms, regardless of whether objective testing data are normal or reveal explanatory pathology, provides patients with valuable clinical reassurance or dictates disease-specific management (i.e., antiarrhythmics, coronary revascularization, etc), respectively, and can do so in a streamlined and time-efficient manner.[18,20–24] In the present study, the addition of customized exercise testing was associated with both outcomes in approximately equal numbers.

In contemporary sports cardiology practice, the diagnosis or exclusion of potentially high-risk cardiovascular conditions as a cause of patients' symptoms is required to facilitate safe and effective return to exercise training or competition. However, the importance of symptom reproduction may be equally relevant in more typical practice settings, as it has the potential to improve care efficiency, reduce costly and invasive subsequent testing, and thereby improve patient satisfaction.[25] Although further study is required to assess these downstream outcomes, our data demonstrate the potential diagnostic yield of customized exercise testing in symptomatic patients and thereby substantiate the emphasis placed on this approach in contemporary exercise testing guidelines.[1,24,26]

Data presented in this manuscript are best interpreted in the context of the study design. In this prospective, single-center experience, the decision to proceed to additional customized testing after inconclusive graded exercise was made on a case-by-case basis, thereby introducing potential selection bias, and the exact diagnostic yield may differ in different clinical settings. It is possible that our results may be skewed toward a higher yield due to our athletic population, as less active patients may experience symptoms at lower workloads that are adequately reproduced by a traditional exercise test. However, the initial graded exercise test in our lab is already largely customized with individualized selection of exercise modality and intensity, is completed to maximal effort with objective confirmation, and includes continuous measurement of metabolic gas exchange and selective use of pre- and postexercise spirometry, all of which likely increase diagnostic yield as compared with a typical exercise test. Therefore, exercise labs that conventionally default to a standardized approach such as the Bruce protocol may have greater incremental yield from customized nongraded exercise provocation than we report despite a less active patient population. Finally, given absence of a gold standard for many of the diagnoses in question, we limit ourselves to reporting diagnostic yield rather than test characteristics such as sensitivity and specificity.

In summary, the selective addition of customized exercise provocation after inconclusive maximal-effort graded testing in symptomatic patients provides valuable information either by identifying an important, clinically-actionable condition or by provoking symptoms in the absence of any testing abnormalities and thus allowing for patient reassurance. Current guidelines advocate for the broader principle of individualizing exercise testing to address patient-specific diagnostic goals, but this is done infrequently in clinical practice.[1,6,27] Data presented in this manuscript are the first to demonstrate that goal-oriented customization of exercise testing improves diagnostic yield and strengthens the rationale for this approach in practice.

Disclosures

The authors have no conflicts of interest to disclose.

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