Exercise stress testing has been widely used for decades to aid in the diagnosis and prognosis of coronary artery disease (CAD). The complication rate during standard exercise testing in populations undergoing evaluation of CAD is well described. The 2002 American Heart Association exercise testing guidelines cite an adverse event rate of up to 0.04% or 1 per 2500 tests.1 This figure is drawn from reports of myocardial infarction or death in a 1980 multi-center study in which >500,000 exercise stress tests were considered.2 Other studies have reported similarly low adverse event rates.3–7 Exercise stress test safety depends on the baseline risk of the population. Many of the patients included in these studies were asymptomatic or had atypical chest pain and were low risk or did not have established CAD.

Clinical perspective on p 2472

Cardiopulmonary exercise testing (CPX) with ventilatory gas analysis is an appropriate test for determining functional capacity in a broader population of patients than only those with possible or established CAD. Peak oxygen uptake (VO$_2$) is generally considered the most accurate determinant of functional capacity. Peak VO$_2$ is a powerful predictor of prognosis in CAD8–10 and congestive heart failure (CHF),11–14 is useful for selecting patients for cardiac transplantation,15–16 and represents a noninvasive surrogate for cardiac output.17–18 Measurement of carbon dioxide production (VCO$_2$) in relationship to VO$_2$ can provide information on exercise limitation. National guidelines cite both of the following as Class I indications for CPX: (1) Evaluation of exercise capacity and response to therapy in patients with CHF who are being considered for heart transplantation; (2) Assistance in the differentiation of cardiac versus pulmonary limitations as a cause of exercise-induced dyspnea or impaired exercise capacity when the cause is uncertain.1 Emerging applications of CPX were recently addressed in an American Heart Association Scientific Statement.19 The application of CPX for these indications can involve testing high-risk patient subsets, including patients with valvular heart disease, hypertrophic cardiomyopathy (HCM), congenital heart disease, and pulmonary hypertension.20–24 Many of these conditions are considered relative contraindications to exercise testing. As such, there is limited published data addressing the safety of CPX in these patient subsets.25–27

The purpose of this study was to examine the safety of CPX in a large, heterogeneous cohort of high-risk patients with a wide variety of underlying high-risk cardiovascular diagnoses.

Methods

Study Population
All patients who were referred for CPX at the Mayo Clinic in Rochester, Minnesota from November 2007 through March 2010

Conclusion—CPX is generally a safe procedure, even in a population with underlying high-risk cardiovascular diagnoses. (Circulation. 2012;126:2465-2472.)

Key Words: complications ■ exercise ■ exercise test ■ heart diseases

The Safety of Cardiopulmonary Exercise Testing in a Population With High-Risk Cardiovascular Diseases

Joseph Skalski, MD; Thomas G. Allison, PhD, MPH; Todd D. Miller, MD, FAHA

Background—Cardiopulmonary exercise testing (CPX) with measurement of peak oxygen uptake (VO$_2$) is a powerful test for assessment and quantification of functional impairment resulting from cardiovascular disease. The safety of CPX has been established in patients with coronary artery disease and congestive heart failure, but clinical use of CPX in other cardiovascular diseases has been limited, in part because of a paucity of safety data. This study investigates the safety of CPX in a heterogeneous cohort of patients with a wide variety of underlying high-risk cardiovascular diagnoses.

Methods and Results—This single-center retrospective review examined 5060 CPX studies performed in 4250 unique patients, including 1748 (35%) female subjects and 686 (14%) subjects aged ≥75 years. The primary end point was major adverse event during stress testing. The study population included patients with a variety of high-risk cardiac diseases, including congestive heart failure (n=1289, 25.5%), hypertrophic cardiomyopathy (n=598, 11.8%), pulmonary hypertension (n=194, 3.8%), and aortic stenosis (n=212, 4.2%). This patient population generally had severe functional impairment, including 1192 (24%) patients with peak VO$_2$<14 mL/kg/min. Eight adverse events occurred during CPX, for an adverse event rate of 0.16%. The most common adverse event (n=6) was sustained ventricular tachycardia. There were no fatal events.

The 2002 American Heart Association exercise testing guidelines cite an adverse event rate of up to 0.04% or 1 per 2500 tests.1 This figure is drawn from reports of myocardial infarction or death in a 1980 multi-center study in which >500,000 exercise stress tests were considered.2 Other studies have reported similarly low adverse event rates.3–7 Exercise stress test safety depends on the baseline risk of the population. Many of the patients included in these studies were asymptomatic or had atypical chest pain and were low risk or did not have established CAD.

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The purpose of this study was to examine the safety of CPX in a large, heterogeneous cohort of high-risk patients with a wide variety of underlying high-risk cardiovascular diagnoses.

Methods

Study Population
All patients who were referred for CPX at the Mayo Clinic in Rochester, Minnesota from November 2007 through March 2010
were retrospectively identified through a computer database. This time period was selected to reflect the expanded use of CPX to include a heterogeneous population of patients with high-risk cardiovascular conditions. The database contains demographic data, cardiovascular medical history, medications, and stress test results. Cardiovascular diagnoses for each patient are identified at the time of testing by reviewing the electronic medical record to determine diagnoses issued by the referring clinician. Initial interrogation of the database yielded 6,136 cardiopulmonary exercise tests, which represents the total number of tests performed during the study period. CPX performed on subjects with no established cardiovascular disease were excluded from the analysis (n = 1,079), excluding patients with only pulmonary or other noncardiovascular disease (n = 805) or athletes undergoing a fitness assessment (n = 274). All other patients who underwent CPX during this time period were included. A total of 5,060 cardiopulmonary exercise tests were identified. For patients who underwent CPX multiple times during the study period (n = 810), all tests are included. The data are reported per each unique stress test rather than per each unique patient because patient characteristics such as cardiac diagnoses, medications, and cardiac device status were all subject to change over the 29-month study period. Furthermore, each individual test presented an additional potential for an adverse event.

To further characterize severity of cardiovascular disease in the study population, echocardiogram data for patients with diagnoses of congestive heart failure, pulmonary hypertension, aortic stenosis, and HCM were reviewed. Echocardiograms performed from 12 months before the CPX date through 1 week after the CPX date were identified. If multiple echocardiograms were performed during that period, the echocardiogram closest to the CPX date was selected. If no echocardiogram was identified within this period, the patient was recorded as having no recent echocardiogram. Patients with aortic stenosis were categorized as mild, moderate, or severe based on echocardiogram results: severe, aortic valve area < 1.0 cm² or mean aortic valve gradient > 40 mm Hg; moderate, aortic valve area ≥ 1.0 and ≤ 1.5 cm² or mean aortic valve gradient ≥ 25 and ≤ 40 mm Hg; mild, aortic valve area > 1.5 and < 3.0 cm² or mean aortic valve gradient ≥ 5 and < 25 mm Hg. Patients with hypertrophic cardiomyopathy were categorized as having basal obstruction, labile obstruction, or no obstruction based on their resting and provoked gradients measured by the left ventricular outflow tract peak instantaneous Doppler gradient. Physiologically provoked gradient refers to the gradient measured during exercise, Valsalva maneuver, or amyl nitrite administration. Patients with resting gradient ≥ 1.0 mm Hg were categorized as having no obstruction; patients with resting gradient < 30 mm Hg but provoked gradient ≥ 30 mm Hg were categorized as having labile obstruction; patients with resting and provoked gradients < 30 mm Hg were categorized as having no obstruction.

Performance of CPX

In the Mayo CPX laboratory both standard and CPX are performed in the same corridor in 7 separate rooms. The testing environment is supervised by a PhD clinical exercise physiologist and a cardiologist. The exercise physiologist assists testing personnel with decisions about test protocol and interprets respiratory gas exchange data. All tests are conducted by a 2-person team, consisting of an exercise specialist and an ECG technician. All exercise specialists have the following qualifications: (1) certified exercise specialist by the American College of Sports Medicine or a registered nurse with coronary care certification; (2) advanced cardiac life support certification; and (3) successful completion of a 3-month internal training program. Each exercise specialist typically performs 2 to 5 cardiopulmonary exercise tests each day. Some of the specialists have > 20 years of experience performing CPX. Although each individual cardiopulmonary exercise test is not directly observed by a cardiologist, a cardiologist is assigned to the CPX laboratory and is available in the immediate area for pretest evaluation of selected patients and to assist in the event of an emergency. The cardiologist is notified before testing if a patient presents with a new finding (such as accelerating symptoms, uncontrolled blood pressure, new ECG changes) that has developed since his or her clinical appointment.

The majority of patients (n = 4,307, 85%) underwent exercise on a motor-driven treadmill (Quinton, Seattle, WA). The remaining patients underwent cycle ergometry. A 3-lead ECG was recorded continuously, and a 12-lead ECG was recorded every minute using a General Electric CASE 8000 (Milwaukee, WI) system. Expired gas collection was performed on a Medical Graphics Corporation (MGC) system (St. Paul, MN). Oxygen saturation was monitored via forehead oximetry using a Nellcor N-595 (Pleasanton, CA). In selected patients, a resting forced vital capacity was performed on the MGC system pre- and 15 minutes postexercise. Most patients (n = 4,116, 81%) exercised using an accelerated Naughton protocol consisting of 2-minute duration stages beginning at approximately 2.5 metabolic equivalents and increasing by 2 metabolic equivalents per stage as previously described.30 The remaining patients exercised using a standard Naughton protocol or Naughton 1.5 protocol (treadmill speed 1.5 mph instead of 2.0 mph). Patients were asked about symptoms at each stage of the test; severity of responses were recorded on a 1 to 10 scale used throughout Mayo Clinic. Patients were encouraged to perform a symptom-limited maximal test (rating of perceived exertion ≥ 17/20 Borg scale),31 unless they met another indication for test termination, including development of significant angina, hypotensive blood pressure response (defined as a drop in systolic blood pressure > 10 mm Hg below resting blood pressure), horizontal or downsloping ST depression of ≥ 2.0 mm, or ventricular tachycardia of > 5 beats in duration.

Interpretation of CPX

All test results were reviewed by the supervising cardiologist and exercise physiologist. The cardiologist interpreted the exercise ECG, whereas the exercise physiologist interpreted the gas exchange data. The exercise ECG was considered ischemic if there was ≥ 1.0 mm horizontal or downsloping ST-segment depression 0.08 seconds after the J-point in the absence of significant resting ST-T abnormalities, preexcitation, ventricular pacing, digitalis, or left bundle branch block. Heart rate recovery was calculated by subtracting heart rate at 1 minute after peak exercise during active recovery (1.7 mph/0% grade) from heart rate at peak exercise. Heart rate recovery of < 13 beats per minute was defined as abnormal.32 Quality of exercise effort was assessed by respiratory exchange ratio (RER), calculated using the formula VO₂/VO₂.

Identification of Adverse Events

For the purposes of this study, a single individual reviewed all CPX reports. The occurrence and nature of all adverse events were documented. In subjects in whom an adverse event occurred, the electronic medical record was examined in further detail to create a narrative description of the adverse event and its outcome. An adverse event was defined as any one of the following: (1) death within 48 hours of the stress test; (2) external defibrillation or implantable cardioverter-defibrillator discharge; (3) sustained ventricular tachycardia (wide complex tachycardia lasting longer than 30 seconds); (4) myocardial infarction; (5) syncope; (6) administration of advanced cardiac life support medications; (7) referral for direct hospital admission; and (8) referral for emergency department evaluation. The latter 2 adverse event criteria were included to ensure that acute situations that might not have fallen into any of the other categories were captured.

Statistical Analysis

All descriptive analyses were performed using the Statistical Analysis System version 9.1 (SAS Institute Inc., Cary, NC) and Excel 2010 (Microsoft Corporation, Redmond, WA). Categorical variables are presented as actual numbers and percentages. Continuous variables are reported as mean ± SD.

Results

Clinical Characteristics

Clinical characteristics are described in Table 1. Mean age was 57.0 ± 15.9 years, including 1847 (37%) patients aged
Table 1. Patient Characteristics: Demographics (n=5060 Tests, 4250 Patients)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
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<tr>
<td>Female</td>
<td>1748</td>
<td>34.5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
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<td></td>
</tr>
<tr>
<td>Tobacco smoking</td>
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<td></td>
</tr>
<tr>
<td>Current</td>
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<td>5.3</td>
</tr>
<tr>
<td>Former</td>
<td>2113</td>
<td>41.8</td>
</tr>
<tr>
<td>Never</td>
<td>2677</td>
<td>52.9</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
<td></td>
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<tr>
<td>Hyperlipidemia</td>
<td>2608</td>
<td>51.5</td>
</tr>
<tr>
<td>Hypertension</td>
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<td>44.9</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>702</td>
<td>13.9</td>
</tr>
<tr>
<td>Medications</td>
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<td></td>
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<tr>
<td>β-blocker</td>
<td>3119</td>
<td>61.6</td>
</tr>
<tr>
<td>Aspirin</td>
<td>2731</td>
<td>54.0</td>
</tr>
<tr>
<td>Statin</td>
<td>2582</td>
<td>51.0</td>
</tr>
<tr>
<td>ACE-I or ARB</td>
<td>2423</td>
<td>47.9</td>
</tr>
<tr>
<td>Diuretic</td>
<td>1982</td>
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<td>Anticoagulant</td>
<td>1151</td>
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<tr>
<td>Calcium channel blocker</td>
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<td>14.7</td>
</tr>
<tr>
<td>Antiplatelet (other than aspirin)</td>
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<td>14.2</td>
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<tr>
<td>Digoxin</td>
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<td>11.3</td>
</tr>
<tr>
<td>Long-acting nitrate</td>
<td>267</td>
<td>5.3</td>
</tr>
<tr>
<td>None of these medications</td>
<td>442</td>
<td>8.7</td>
</tr>
</tbody>
</table>

Continuous variables are reported as mean±standard deviation. BMI indicates body mass index; ACE-I, angiotensin converting enzyme inhibitor; and ARB, angiotensin II receptor blocker.

≥65 years and 686 (14%) patients aged ≥75 years. Approximately one-third of the population was female. The mean number of medications at the time of CPX was 3.2±1.9. β-Blockers were the most common drug (61.6%), reflecting the large number of patients with CAD or left ventricular dysfunction. Only 8.7% of patients were not taking any cardiovascular medications at the time of their CPX. The majority of patients taking no cardiovascular medications at the time of their CPX had congenital heart disease, valvular heart disease, or arrhythmia that was not being managed pharmacologically.

Table 2 lists cardiac diagnoses. Some patients had ≥1 diagnosis. Approximately one-quarter (25.5%) of the study population had CHF on the basis of CAD (8.9%) or no CAD (16.6%). Approximately one-quarter (27.4%) had valvular heart disease, including 4.2% with aortic stenosis. Other structural heart disorders included congenital heart disease (13.6%), HCM (11.8%), and cardiac transplantation (7.3%). A total of 1012 patients (20.0%) had an implanted cardiac device (implantable cardioverter-defibrillator or pacemaker), and 453 patients (9.0%) were in chronic atrial fibrillation or flutter. There were 65 (1.3%) patients with renal transplant and 26 (0.5%) patients with liver transplant. The patients with congenital heart disease included a heterogenous group of underlying disorders. Among the 688 patients with congenital heart disease, 463 (67%) had undergone ≥1 open cardiac operations in their lifetime, suggesting severe disease.

Table 3 lists echocardiogram data for patients with diagnoses of CHF, pulmonary hypertension, aortic stenosis, or HCM. Two hundred eighty-six patients (5.7% of total, 22.2% of CHF patients) had severe left ventricular systolic dysfunction, as indicated by left ventricular ejection fraction ≤25%. The study cohort included 300 patients (6.0% of total, 23.3%
of CHF patients) with CHF with preserved ejection fraction. Ninety patients (1.8% of total, 42% of aortic stenosis patients) had severe aortic stenosis. More than half of the pulmonary hypertension patients had an estimated right ventricular systolic pressure >40 mm Hg. Among HCM patients, 150 (3.0% of total, 25.1% of HCM patients) had baseline obstruction. Among these patients, 142 had a resting or provoked gradient of ≥50 mm Hg, indicating severe obstruction. An additional 89 HCM patients (1.8% of total, 14.9% of HCM patients) had labile obstruction.

### CPX Results

Table 4 and Figure 1 describe the stress test results. The majority of patients (n=4783, 94.5%) completed symptom-limited CPX with termination of the test resulting from symptoms of fatigue, dyspnea, or chest pain. In the remaining 5.5% of patients, the test was terminated as a result of ECG changes, abnormal blood pressure response, patient request, or major adverse event.

Almost one quarter of patients (24%) had peak VO	extsubscript{2} <14 mL/kg/min, consistent with severe functional impairment. Effort was generally good, with a mean peak RER 1.18±0.11. Nearly half of patients were observed to have abnormal heart rate recovery. Only 129 patients (2.5%) had an exercise ECG positive for ischemia. Because of a large number of patients with abnormal resting ECG, 38% of stress ECGs were reported as nondiagnostic. Resting ECG abnormalities included 285 (5.6%) patients with left bundle branch block and 562 (11.1%) patients with paced rhythm.

### Adverse Events

Figure 2 displays adverse events. Eight adverse events occurred, yielding a rate of 0.16%. Table 5 contains a narrative description of the adverse events. Six of the 8 events resulted in hospitalization. There were no fatal events. Although ≈10% of patients had an implantable cardioverter-defibrillator at the time of their study, no implantable cardioverter-defibrillator discharges occurred during stress testing. No patient experienced syncope. Six of the events (n=6) were sustained ventricular tachycardia. All terminated spontaneously without defibrillation or advanced cardiac life support medications. Four of the 6 episodes of ventricular tachycardia led to hospital admission, and the other 2 episodes were managed with close outpatient follow-up. One patient with known CAD developed severe and persistent dyspnea and was admitted for observation without objective evidence for a new cardiac event.

The single myocardial infarction occurred in a 53-year-old man who had received cardiac transplant 6 years before and was undergoing surveillance CPX as part of routine post-transplant follow-up. He had not been experiencing chest pain, dyspnea, or other concerning symptoms in the outpatient setting before his stress test. During the stress test he abruptly developed severe anginal pain and ST segment elevation on the cardiac monitor after 10.4 minutes of exercise. He was taken emergently to the cardiac catheteriza-
tion laboratory, where a new 90% stenosis was noted in his first obtuse marginal coronary artery. A drug-eluting stent placement was performed. He was discharged from the hospital in stable condition.

**Discussion**

Earlier studies examining the safety of exercise testing were performed primarily in patient populations undergoing evaluation of possible CAD. Many patients in these studies were asymptomatic or had atypical symptoms and likely did not have CAD, diluting the denominator and leading to very low reported complication rates for standard exercise testing. Conversely, in the present study nearly all patients had known structural heart disease. The most important finding of this study is the very low adverse event rate of only 0.16% in a much higher risk population undergoing CPX. There were no fatal complications. A strength of this data set is the heterogeneity of the study population, which included a wide variety of underlying cardiac diagnoses. Many of these disorders are considered relative contraindications to exercise testing. In this study, 19% of the population had HCM, pulmonary hypertension, or aortic stenosis. None of the adverse events occurred in patients with any of these conditions.

The mean peak VO\(_2\) across all patients was only two-thirds of predicted, reflective of significant impairment in functional capacity for this population. Almost one quarter (23.5%) were found to have severely limited functional capacity as indicated by peak VO\(_2\)<14 mL/kg/min. This value is the threshold that is often used to determine which CHF patients are eligible for heart transplantation. The majority of the patients (n=3210, 64%) exercised to an RER >1.15, suggesting maximal exertion.

Because of their severe functional impairment, some patients in this study would likely be candidates for disability resulting from cardiac disease. According to an Institute of Medicine panel recently convened to advise the Social Security Administration on cardiovascular disability, CPX should be the procedure of choice for assessing cardiovascular disability. CPX provides the most accurate means of quantifying functional impairment. Measurement of the RER represents the most objective method of assessing effort exerted during an exercise test, thereby providing a means to detect individuals who are intentionally underperforming in an attempt to game the system. However, stress testing is not widely applied for disability assessment, in part because of concerns about safety of testing in high-risk populations. The results of this study will hopefully encourage increased use of CPX for this purpose.

Another notable finding from this study is that only 129 (3%) patients had a positive exercise ECG. The relatively low number of positive stress ECGs was attributable in part to the substantial number of patients with an abnormal resting ECG, which precluded interpretation of the exercise ECG. Accounting for overlap of patients with multiple rhythm disorders, a total of 830 (16.4%) patients had an ECG demonstrating left bundle branch block, paced rhythm, or Wolff-Parkinson-White at rest. In 38% of
patients the stress ECG was reported as nondiagnostic. Other reasons for the low number of positive stress ECGs include the average low functional capacity of the study population and referral generally for quantification of cardiopulmonary functional impairment rather than detection of ischemia. The low yield of positive exercise ECGs in this population should not undermine the value of the exercise ECG for detecting ischemia in patients undergoing stress testing for evaluation of chest pain.

Other authors have reported on the safety of CPX in high-risk populations. In the Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) study, Keteyian et al examined 2037 subjects with left ventricular dysfunction (median left ventricular ejection fraction 25%) who underwent CPX on multiple occasions.25 There were no fatal events and only 2 episodes of ventricular arrhythmia among 4411 exercise tests. Scardovi et al examined 227 elderly patients with CHF who underwent 395 cardiopulmonary exercise tests.26 No adverse events were observed. Sun et al also noted no adverse events in 53 patients with primary pulmonary hypertension who underwent CPX.27

The unique aspects of the present study include the larger size of the study population and the heterogeneity of cardiovascular disorders present.

This study has limitations. This data set includes stress tests performed at a single academic tertiary care medical center, which limits the extent to which our observed safety data can be generalized. However, it is reassuring that these results are consistent with CPX safety data reported from other institutions. Nearly all patients were first assessed by a cardiologist and felt to be stable enough to be referred for CPX. There are limitations with the database to extensively characterize the study population. Some patients did not undergo additional diagnostic testing, such as echocardiography in close proximity to CPX. Thus, additional data to quantify the severity of left ventricular systolic dysfunction, pulmonary hypertension, or valvular dysfunction (such as severity of aortic stenosis) cannot be reported for the entire study population.

This study was not designed to determine whether any underlying attribute or cardiovascular disease confers a higher risk of adverse event during CPX than others. Interestingly, all 8 of the adverse events occurred in males. Most
(6 of 8) adverse events noted in our study were ventricular arrhythmia. Some observational studies do suggest that there is a higher rate of sudden cardiac death and ventricular arrhythmia in men compared with women.33,34 However, the conclusion that men are at greater risk than women of adverse event during CPX cannot be drawn from this study.

The major value of this article is the demonstration that CPX is a reasonably safe procedure in a population of patients with a spectrum of established cardiovascular diseases, many of which represent high-risk conditions and are considered relative contraindications to stress testing.1 It is important to recognize that all of the patients in this study had their cardiovascular diagnoses established before CPX, and that testing was carefully performed in an experienced laboratory at a tertiary care center. There are subsets of patients with the most extreme variants of these conditions, in whom stress testing represents an absolute contraindication, such as a patient with severe symptomatic aortic stenosis. However, for other patients with these disorders, CPX appears to be reasonably safe and can serve as a helpful aid in the management of these patients. Given the low event rate in this study, a larger population would be necessary to determine which of these patients are at highest risk of experiencing a complication during CPX.

Disclosures
Dr Miller has consulting arrangements with Astellas Pharma and Lantheus Medical Imaging and receives research funding from Forest Laboratories. The other authors report no conflicts.

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**CLINICAL PERSPECTIVE**

Cardiopulmonary exercise testing (CPX) with measurement of peak oxygen uptake (Vo2) is the most accurate test for quantification of functional impairment resulting from cardiovascular disease. CPX has primarily been applied in patients with congestive heart failure to help select candidates for heart transplantation. There are other cardiovascular disorders (aortic stenosis, hypertrophic cardiomyopathy, pulmonary hypertension, and congenital heart disease) for which accurate assessment of functional capacity could serve as a useful aid in the clinical management of these patients. However, CPX has not been widely applied in these patient subsets, in part because of limited availability of safety data. This study investigated safety of CPX in 4250 patients with a wide variety of underlying high-risk cardiovascular diseases who underwent a total of 5060 tests. CPX was found to be reasonably safe in this study cohort, with an adverse event rate of 0.16% and no fatal events. This research may lead to further clinical application of CPX in these patient subsets.

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