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Obese sedentary patients with dyspnoea on exertion who are at low risk for coronary artery disease by clinical criteria have a very low prevalence of coronary artery disease

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Summary

Dyspnoea, a much less specific symptom of ischaemia than chest discomfort, is common among obese patients. Patients with dyspnoea often undergo stress testing as part of their evaluation. We sought to examine the yield of stress testing in non-elderly, obese, sedentary patients with dyspnoea on exertion (DOE) as a chief complaint.We reviewed stress echocardiograms carried out on 203 patients in a stress testing laboratory at a major tertiary care centre. Of these, 81 (40%) fell into a group that was at low risk for coronary artery disease (CAD) by clinical criteria. Ischaemia was detected in two patients in the low-risk group (2.5%), and these results were likely false positives. In the higher risk group, 9.0% of functional tests showed ischaemia; after further testing, 2.5% of the higher risk patients were found to have obstructive coronary lesions. Clinical follow-up was performed for a mean of 815 days. New obstructive coronary disease was detected in 1.6% of all patients, and these patients were from the higher risk group. In obese sedentary patients with DOE but otherwise at low risk of coronary disease stress testing is of very low yield. DOE is generally not an anginal equivalent in this patient population.

Keywords: Coronary artery disease, dyspnoea on exertion, stress echocardiography.

Introduction

Dyspnoea on exertion (DOE) is a non-specific symptom (1). In some cases dyspnoea seems to represent an anginal equivalent (2–5), and in patients at elevated risk for CAD, dyspnoea may predict higher rates of cardiac death and non-fatal myocardial infarction (6–13), although not all studies confirm this finding (14), and worse outcomes may not be linked to a greater burden of ischaemia (15,16). Concern about DOE as an anginal equivalent is often extended to patients who are not at high risk for coronary artery disease (CAD) by clinical criteria, and limited data suggest that such patients may not in fact have an increased prevalence of CAD (17). There is little guidance from the literature regarding stress testing in patients at low risk for CAD who have DOE. The most recent American College of Cardiology/American Heart Association Guideline for Exercise Testing does not discuss pre-test probability of dyspnoea as a symptom of CAD (18). The 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging acknowledges that dyspnoea can be an anginal equivalent, but no specific recommendations regarding testing are given (19). In a population with a low prevalence of the condition for which testing is being performed, most positive tests will be false positives (20,21). This results in further testing, with increased expense to society and increased risk to patients.

Table 1 Patient characteristics

Risk factors and clinical presentation	*n* or mean	% or IQR*
Male	101	49.8%
Age	46.2	43–51
BMI	37.6	33.0–39.8
History of CAD	14	6.9%
Cerebrovascular disease	1	0.5%
Diabetes		
All	41	20.2%
On insulin	18	8.9%
Family history	31	15.3%
Smoking history		
All	76	37.4%
Current smoking	33	16.3%
Hypertension	111	54.7%
Dyslipidaemia	140	69.0%
Framingham score	3.6	1–5
Typical angina	9	4.4%
Abnormal resting ECG	57	28.1%
Q wave	22	10.8%
T-wave inversion	24	11.8%
ST-segment depression	1	0.5%
LV hypertrophy	12	5.9%

*Interquartile range (25–75%ile).
BMI, body mass index; CAD, coronary artery disease; ECG, electrocardiogram; LV, left ventricular.

We determined the prevalence of CAD in a group of patients with DOE but otherwise at low risk for CAD. We chose to evaluate a group with alternative explanations for DOE. We reviewed stress tests and performed chart review on non-elderly, obese, sedentary patients for whom the stress test indication was dyspnoea. We identified patients in this group who were at low risk for CAD using usual clinical criteria. Patients at increased risk were evaluated in parallel. Outcomes suggesting CAD as a cause of DOE included ischaemia on stress testing, CAD by catheterization and coronary events occurring during follow-up. The hypothesis was that DOE is not generally an anginal equivalent in clinically low-risk groups, particularly if there is an alternative explanation for DOE, and that testing for CAD as the cause of DOE (specifically with stress echocardiograms) is not helpful in evaluating DOE in this population.

Methods

Population

The University of Michigan maintains a computer database of all echocardiographic stress tests that includes body mass index (BMI), activity level (with 'sedentary' as one category) and indication for the test. This database was queried to identify all patients younger than age 55, with BMI greater than 30, and listed as having a sedentary lifestyle as assessed by the exercise physiologist, for whom the test indication was dyspnoea. Patients were judged to be sedentary if they did not have any regular significant level of physical activity [e.g normal levels of activity less than about four metabolic equivalents (METs)] either at work or at home. A cross-sectional (for initial follow-up testing) and retrospective cohort (for longitudinal follow-up) design was utilized. Tests performed from October 2007 to January 2011 were evaluated.

Baseline risk factors

Records were reviewed to clarify the character of the patient's presenting symptoms (presence or absence of chest pain and its character, dyspnoea and symptom severity). Patients for whom DOE was the chief complaint, as assessed by chart review, were included in the study. Patients with chest discomfort suggestive of angina were assigned to the higher risk group. The medical history was evaluated for indicators of increased risk, including coronary disease (with or without previous revascularization), diabetes mellitus (and whether there was a requirement for insulin), hypertension (and/or requirement for antihypertensive medication), cerebrovascular disease, past or active smoking, and family history of premature CAD (first-degree relatives with coronary disease before 55 in men or before 65 in women). Patients with any of these findings were assigned to the higher risk group. The physical examination was evaluated for abnormalities, principally cardiac murmurs and rales. The resting electrocardiogram (ECG) was evaluated for abnormalities suggestive of ischaemia or other significant pathology; specifically, Q waves, abnormal T-wave inversion, right or left ventricular hypertrophy (LVH), tachycardia of any type including sinus tachycardia (22), premature ventricular contractions, atrial fibrillation, atrioventricular block of any degree, bundle branch block or intraventricular conduction delay. Baseline risk factors were used to calculate Framingham 10-year risk scores (23). Patients with any of these abnormalities on physical examination or ECG, or who had a 10-year risk of 10% or more of adverse cardiac events by Framingham scoring, were assigned to the higher risk group. (Patient characteristics are shown in Table 1.)

Stress testing

Exercise and dobutamine stress echocardiograms were conducted according to standardized procedures utilized throughout the health system. Standard exercise stress protocols were used (24). The adequacy of the exercise tests was judged according to the level of cardiac stress (a pressure–rate product of >250 mmHg × beats min^{-1}) and the exercise tolerance (average or greater, determined by number of METS on an age-based nomogram).

Dobutamine stress tests were deemed adequate if the patient's maximum heart rate recorded was >85% of the age-predicted maximum heart rate (calculated as 220 – [patient's age]).

Echocardiography

Echocardiographic information was reviewed. The primary finding for which the tests were evaluated was the presence of new or worsening regional wall motion abnormality with stress. Fixed wall motion abnormalities consistent with regions of previous infarction were also noted. The resting echocardiogram was evaluated for alternative explanations for dyspnoea, including severe pulmonary hypertension, moderate or severe valvular stenosis or regurgitation, evidence of cardiomyopathy [ejection fraction (EF) 40% or less], diastolic dysfunction (and its grade) and more than mild right heart dilation.

Follow-up testing

Charts were reviewed for follow-up testing, particularly cardiac catheterizations and nuclear perfusion scans. Test results were examined for evidence of new obstructive coronary lesions judged likely to be responsible for symptoms. Charts were also reviewed for assessment by the ordering clinician whether a clinically significant cause of the dyspnoea was found. The records were examined longitudinally to determine whether any patients experienced subsequent cardiovascular events in the post-testing period. Episodes of heart failure, myocardial infarction, revascularization or cardiac surgery were noted. All patients, including those with inadequate stress tests, were followed.

Statistical analysis

Continuous variables were reported as mean with 95% confidence interval (CI). Comparisons between means were performed according to the Student's *t*-test. Categorical variables were compared according to the chi-squared test (or Fisher's exact test for categorical variables with less than five observations). Analysis of time to event data was performed using a univariate Cox model. Because of the low event rate, Cox models beyond one predictor could not be created. Statistical significance from the Cox models were assessed using the likelihood ratio test (favoured for small sample sizes). Hazard ratios could not be estimated from the model due to no observed events in the low-risk group. Statistical significance was determined at the $P < 0.05$ level. Statistical analysis was performed on the JMP Platform (version 10; SAS Institute, Cary, NC, USA) for descriptive analyses and SAS 9.3 ×64 Platform for Cox model.

Results

There were 244 patients identified by the echocardiography database who met the initial inclusion criteria of age less than 55, BMI greater than 30 and sedentary lifestyle. Of these, 203 (83.2%) patients were eligible for inclusion into the final data analysis and 41 (16.8%) were excluded (Fig. 1). The primary reasons for exclusion were missing data (in 20 patients), referral from outside the health system so that progress notes and records were not available for review (11 patients), and testing performed for known disease, including pulmonary hypertension, hypertrophic cardiomyopathy (HCM) and ischaemic cardiomyopathy (nine patients). Among the 203 included patients, the most frequent referring specialties were general internal medicine (105 patients, 51.7%), family medicine (39 patients, 19.2%) and cardiology (32 patients, 15.8%), as shown in Fig. 2. There were a smaller proportion of patients referred from medical subspecialty clinics and from surgery/anaesthesiology. One patient was referred from the emergency department.

Patient risk factors

Patients were assessed for factors that would affect pre-test probability for CAD (see Baseline Risk Factors in Methods section above). Patients with none of these factors were taken to be the low-risk group. A total of 81 patients (39.9% of the total sample) were assigned to the low-risk group.

Testing modalities

The stress modality was treadmill exercise echo in 156 patients (76.8%) and dobutamine echo in 47 patients (23.2%). Stress tests were inadequate to assess for ischaemia in a total of 47 patients, either because of inadequate workload attained or because of inadequate images. Seventeen patients in the treadmill group failed to reach adequate stress thresholds. Twenty patients in the dobutamine group failed to reach target heart rate. There were 12 patients with poor quality echocardiogram images. Two of these 12 patients also had inadequate workload achieved on stress testing. There was no difference in adequacy of imaging between the low-risk and high-risk groups. In the higher risk group, 27.1% of tests were inadequate and 17.3% were inadequate in the low-risk group (odds ratio 1.77; 95% CI 0.88–3.6; $P = 0.13$ by Fisher's exact test). Follow-up non-invasive testing was performed in 10 patients due to inadequate echocardiographic stress tests.

Initial test results

In total, there were 13 (6.4%) studies with findings consistent with inducible ischaemia. In the low-risk group, two

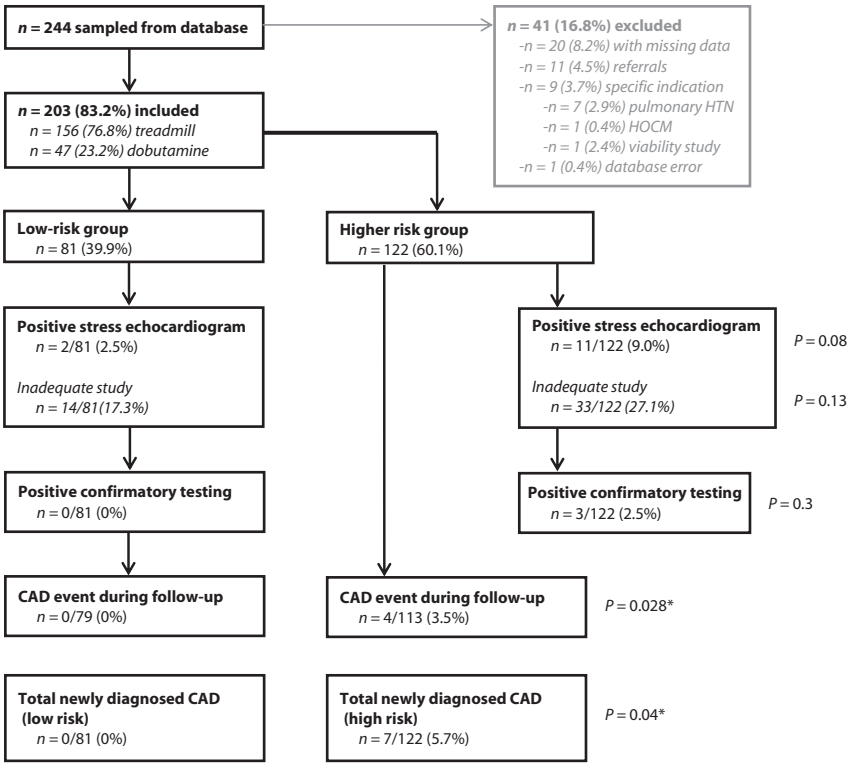

Figure 1 Diagnostic algorithm. CAD, coronary artery disease; HOCM, hypertrophic obstructive cardiomyopathy; HTN, hypertension.

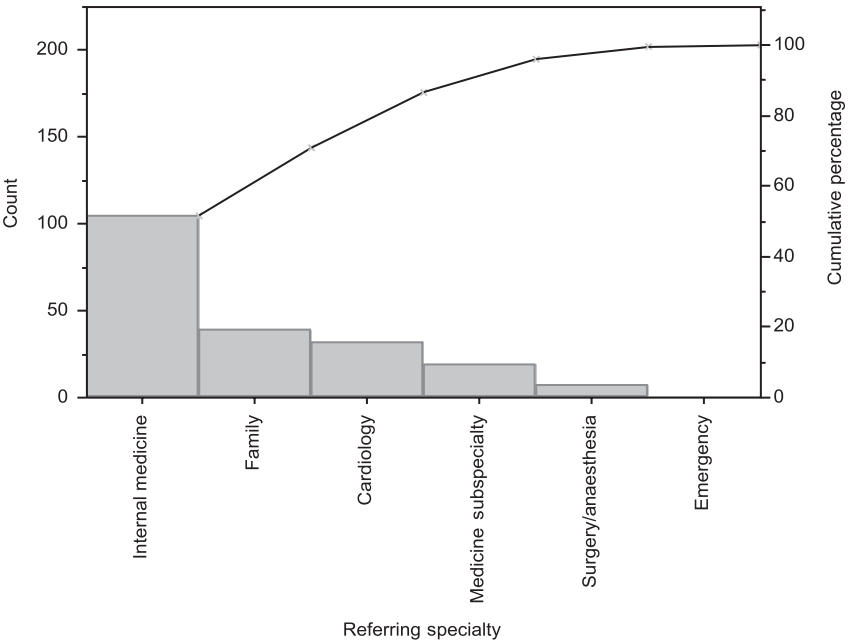

Figure 2 Referring specialties. Pareto chart of referring specialties, showing bar graph of counts and line of cumulative percentage.

patients (2.47%) had positive studies, compared with 11 patients (9.02%) in the higher risk group. There was no statistically significant difference in the rate of test positivity between the low- and high-risk groups ($P = 0.08$ by Fisher's exact test). The overall rate of test positivity was not different between testing modalities (dobutamine vs. exercise).

Confirmatory testing

Immediate follow-up testing (with nuclear perfusion scan or cardiac catheterization) was performed in 11 (84.6%) of the 13 patients with inducible ischaemia. Of the two patients in the low-risk group with positive studies, confirmatory testing was negative in one and was never per-

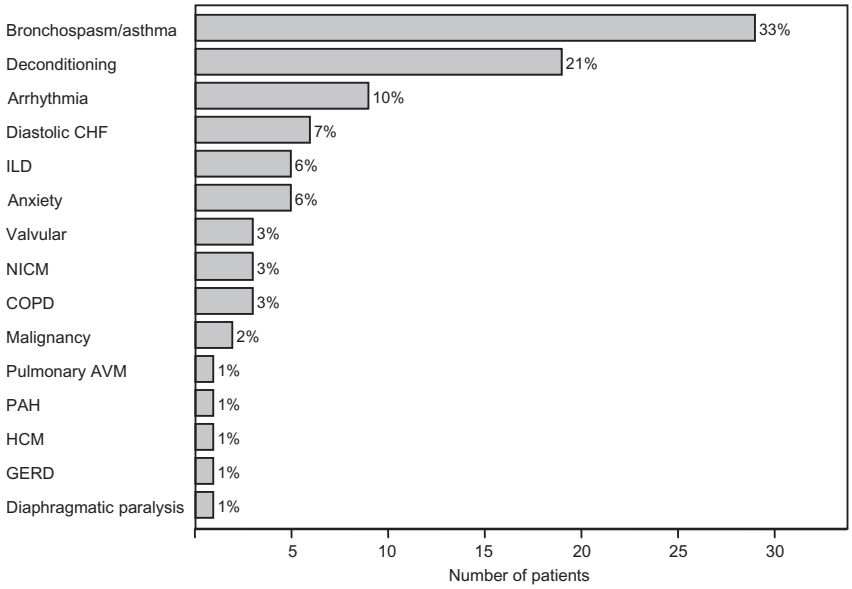

Figure 3 Alternative diagnoses. Bars are labelled with percentage of total. AVM, arteriovenous malformation; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; GERD, gastro-oesophageal reflux disease; HCM, hypertrophic cardiomyopathy; ILD, interstitial lung disease; NICM, non-ischaemic cardiomyopathy; PAH, pulmonary arterial hypertension.

formed in the other, because her symptoms resolved prior to follow-up and never recurred. Hence, no members of the low-risk group were found to have obstructive CAD. In the higher risk group, three patients (2.46%) were ultimately diagnosed with new obstructive coronary lesions by cardiac catheterization. This difference was not statistically significant ($P = 0.3$ by Fisher's exact test).

Although not every patient received confirmatory testing (in this case, nuclear perfusion scanning or diagnostic angiography), the sensitivity, specificity and predictive values of stress echocardiography can be estimated. For all subjects, the estimated sensitivity is 66.7% (95% CI 20.8–93.9%), specificity 94.5% (95% CI 90.4–96.9%). Given the low disease prevalence of 1.5%, the positive predictive value in this population is very low at 15.4% (95% CI 4.3–42.2%).

Alternative diagnoses

The symptoms of 89 patients were ascribed to diagnoses other than CAD during subsequent follow-up (Fig. 3). The alternative diagnoses were frequently pulmonary (in 40 patients), and included asthma or bronchospasm (29 patients), chronic obstructive pulmonary disease (three patients), interstitial lung disease (five patients), pulmonary arteriovenous malformation (one patient) and diaphragmatic paralysis (one patient). Alternative cardiac diagnoses were found in 24 patients, and included diastolic congestive heart failure (diastolic CHF) in six patients, valvular disease in three patients and non-ischaemic cardiomyopathy in three patients. Deconditioning was directly implicated by the referring physician in 19 patients. Symptoms were ultimately attributed to anxiety in five patients.

In some cases the echocardiographic results suggested alternative diagnoses that might account for symptoms. Ejection fraction was <40% in three patients. Severe mitral regurgitation was identified in two patients. No patients had right ventricular (RV) systolic pressure >40 mmHg. There was evidence of RV dysfunction in three patients; RV dysfunction was mild in two of these and mild to moderate in the third. Diastolic dysfunction of grade 2 or greater in severity was present in six patients. LVH was present in 54 patients, but severe LVH was present in only one patient, and that person was subsequently diagnosed with HCM.

Follow-up testing

The 200 patients (98.5%) without obstructive lesions identified on initial evaluation were followed for subsequent development of new obstructive coronary lesions of >70% stenosis by coronary angiography. There were eight patients excluded for lack of follow-up information, for a total of 192 patients with follow-up information available. There was a broad range of follow-up intervals. The median follow-up was 815 days, with a 25–75% interquartile range of 548–1083 days.

In total, there were three (1.56%) patients who developed objectively documented obstructive coronary disease during the follow-up interval. An additional patient had an episode of coronary vasospasm resulting in ST elevation. All of these patients were members of the higher risk group. The difference in rate of detection of obstructive coronary disease between the low and higher risk groups during the follow-up period was statistically significant ($P = 0.028$ by likelihood ratio test), with the lower 95% bound of the hazard ratio of 1.4.

The overall difference in diagnosis of obstructive coronary disease between the low and higher risk groups including initial testing was also statistically significant ($P = 0.04$ by Fisher's exact test).

Comment

This study represents the first analysis of the performance of stress echocardiography in non-elderly, obese, sedentary patients who present with DOE as their sole symptom. A prior study also found stress echo to be of very low yield in low-risk groups, but that study did not assess dyspnoeic patients (25). While patients in the current study were by most standard criteria at low risk for CAD, they had symptoms that are often thought to represent an anginal equivalent. Review of stress echocardiograms performed on the low-risk group reveals a very low rate of apparent ischaemia, and the two tests suggesting ischaemia were in fact most likely false-positive results. No obstructive CAD was found in this group. Event rates in this group were also very low, with no myocardial infarctions occurring during extended follow-up. It is noteworthy that, in the group of patients with markers of higher risk that we evaluated in parallel, the few new obstructive coronary lesions that were detected occurred in patients presenting with typical angina. These findings support guideline recommendations stating that the strongest indication for stress testing and the most specific symptom of ischaemia is chest pain, especially typical angina. Our findings suggest that DOE is not generally an anginal equivalent in patients similar to those studied here, particularly the lower risk group, and that evaluation for CAD with stress echocardiograms is not helpful in patients like those presented here who are at low risk for CAD by usual clinical criteria. It is worth noting in this context that there are data suggesting that obesity actually protects against adverse cardiovascular outcomes (the so-called obesity paradox) (26), and this may help explain the very low rates of ischaemia and acute coronary syndromes detected in our study.

Our data do support alternative testing and management strategies for this population. A much less expensive and potentially higher yield test for aetiologies of dyspnoea, especially in patients at low risk for CAD, is cardiopulmonary exercise testing (CPET), which can be used to assess for pulmonary and cardiac conditions of various types with a single test (27). The high incidence of pulmonary causes of dyspnoea in our low-risk test population suggests that it would have been reasonable to send these patients for CPET or other pulmonary evaluation instead of or prior to standard imaging stress tests. Several patients in the low-risk group also had cardiac abnormalities detected by echocardiogram that might be responsible for dyspnoea, suggesting that resting echocardiographic data might have been helpful in this group. Another reasonable management strategy might be a supervised weight loss and exercise programme with further evaluation dependent on whether symptoms are persistent.

Our evaluation has limitations. This was a single-centre study, and so our findings might not be generally applicable to other institutions, although it is not immediately apparent why this would be true. Our sample size was limited and thus lacked some degree of statistical power. Additionally, the retrospective design could potentially introduce reporting bias. However, a large proportion of the patients had longitudinal follow-up with their primary care physicians within the health system and data were collected prospectively at the time of clinic visits. As expected with stress testing, particularly when testing a group of obese patients, there was a fairly high rate of inadequate stress tests. This may result in underestimation of CAD in the study. However, all of these patients had extended clinical follow-up to determine the subsequent rate of clinical coronary events and to determine the diagnoses that were ultimately felt to explain their symptoms. This adds significant additional information regarding the likely prevalence of CAD in this group.

The work presented here may contribute to safe limitation of stress testing. One way this might be accomplished is by development of a clinical scoring system that would predict risk of CAD in patients with dyspnoea but no chest pain. Scoring systems using specific risk markers have been successfully applied to reduce testing in other medical conditions. One example is the PERC scoring system that is used to risk stratify patients with possible pulmonary embolus (28). A low PERC score defines a group at such low risk of pulmonary embolus that no further testing is recommended or desirable. An analogous scoring system for patients with dyspnoea would be extremely useful, and could serve to limit, in a safe manner, the number of stress tests performed in this group.

Conflict of interest statement

No conflict of interest statement.

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