Title

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Journal

The American journal of cardiology, 111(7)

ISSN

0002-9149

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Publication Date

2013-04-01

DOI

10.1016/j.amjcard.2012.12.023

Accuracy of Stress Myocardial Perfusion Imaging to Diagnose Coronary Artery Disease in End Stage Liver Disease Patients

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Patients with end-stage liver disease (ESLD) who also have underlying coronary artery disease (CAD) may be at increased risk for undergoing hemodynamically challenging orthotopic liver transplantation. Noninvasive single-photon emission computed tomographic (SPECT) imaging is often used to determine whether a patient with ESLD has unsuspected CAD. The objective of this study was to determine the accuracy of SPECT imaging for detection of CAD in patients with ESLD. Patients with ESLD who underwent coronary angiography and SPECT imaging before orthotopic liver transplantation were analyzed retrospectively. The predictive accuracy of clinical risk factors was calculated and compared to the results of SPECT imaging. There were 473 SPECT imaging studies. Adenosine SPECT imaging had a sensitivity of 62%, specificity of 82%, positive predictive value of 30%, and negative predictive value of 95% for diagnosing severe CAD. Regadenoson SPECT imaging had a sensitivity of 35%, specificity of 88%, positive predictive value of 23%, and negative predictive value of 93% for diagnosing severe CAD. The accuracy of a standard risk factor analysis showed no statistical difference in predicting CAD compared with adenosine (sensitivity McNemar's $p = 0.48$, specificity McNemar's $p = 1.00$) or regadenoson (sensitivity McNemar's $p = 0.77$, specificity McNemar's $p = 1.00$) SPECT studies. In conclusion, the 2 pharmaceutical agents had low sensitivity but high specificity for diagnosing CAD. However, because the sensitivity of the test is low, the chances of missing patients with ESLD with CAD is high, making SPECT imaging an inaccurate screening test. A standard risk factor analysis as a predictor for CAD in patients with ESLD is less expensive, has no radiation exposure, and is as accurate as SPECT imaging. **(Am J Cardiol 2013;111:1057−1061)**

In patients with end-stage liver disease (ESLD), the prevalence of coronary artery disease (CAD) increases with age and ranges from 5% to 27%.[1−3] Mortality at 3 years after liver transplantation was reported to be 26% to 50% in patients with CAD, compared with 7% in patients without CAD.[4−6] However, a recent multicenter study showed no difference in mortality between patients with CAD (29%) and those with no CAD (24%) at 3 years, demonstrating improved results with current management of CAD in patients with liver failure.[7] Coronary angiography remains the gold standard to evaluate the presence of CAD in patients with ESLD, but the American College of Cardiology and American Heart Association guidelines consider routine angiography not indicated (class III) for patients who undergo noncardiac surgery unless noninvasive testing reveals high risk for an adverse outcome.[8] In addition, there is an increased risk for bleeding from angiographic procedures in patients with ESLD because of decreased coagulation factors, low platelet count, and increased fibrinolytic activity.[9] As part of the preoperative screening workup, patients may undergo either myocardial perfusion single-photon emission computed tomographic (SPECT) imaging or dobutamine stress echocardiography. The mode of stress for a SPECT study is either exercise or a pharmacologic agent such as adenosine or regadenoson. Studies assessing the diagnostic use of dobutamine stress echocardiography and SPECT in candidates for orthotopic liver transplantation have been inconclusive.[2,10−13] No study has described the accuracy of regadenoson stress tests in patients with ESLD. The aim of this study was to assess the diagnostic accuracy of adenosine or regadenoson SPECT stress tests versus standard risk factor analysis compared to coronary angiography in patients with ESLD who underwent cardiac evaluation for consideration for undergoing orthotopic liver transplantation.

Methods

From 2006 to 2011, all patients with ESLD who were being evaluated for possible liver transplantation were analyzed retrospectively. Patients who underwent angiography and myocardial perfusion imaging were included in this study. The protocol used for the cardiac evaluation for orthotopic liver transplantation candidates at the University of California, Los Angeles, Medical Center is shown in

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See page 1060 for disclosure information.

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http://dx.doi.org/10.1016/j.amjcard.2012.12.023

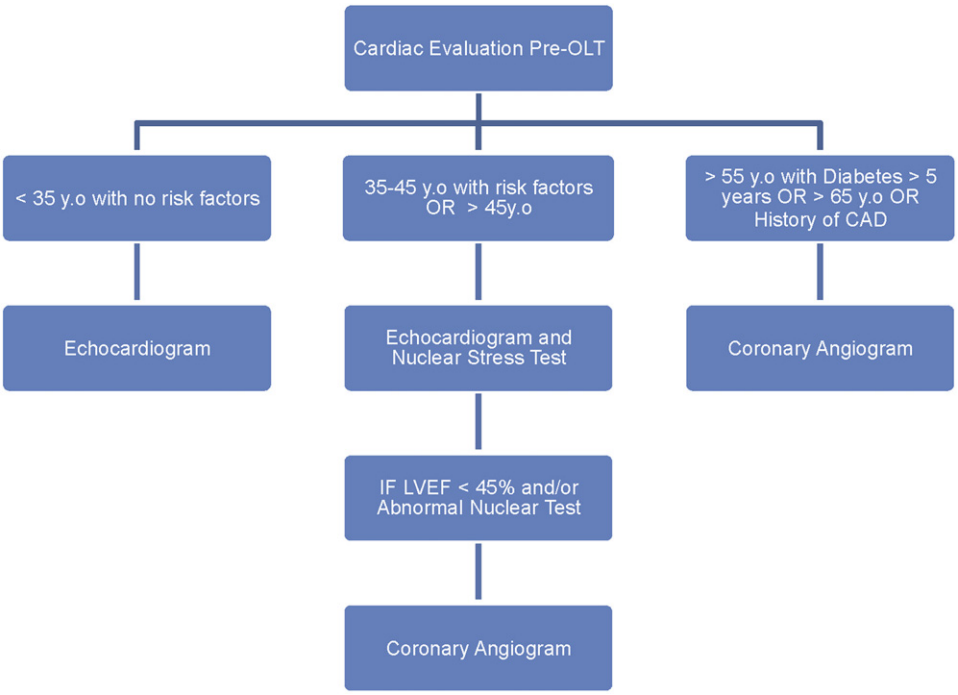

Figure 1. Cardiac evaluation protocol at the University of California, Los Angeles, Medical Center before orthotopic liver transplantation (OLT). LVEF = left ventricular ejection fraction; y.o = years old.

Figure 1. Myocardial perfusion imaging was performed per standard protocols.[14] The initial study involved the intravenous injection of technetium-99m tetrofosmin or sestamibi at rest, followed by imaging 5 to 10 minutes later. The pharmacologic stress agent changed over the time course of the analysis. In patients who underwent stress testing before 2008, the agent of pharmacologic stress was adenosine, given as a continuous infusion at a dose of 140 μg/kg/min over a 6-minute period. After 2008, regadenoson was used as a stressor at a single dose of 0.4 mg given intravenously as a rapid (approximately 10 seconds) injection. Technetium-99m tetrofosmin or sestamibi was injected at peak stress, and standard SPECT images were acquired 60 minutes after the injection. Electrocardiogram, blood pressure measurements, and heart rate were monitored serially during the stress test. The University of California, Los Angeles, institutional review board approved this retrospective study, in which patients records were assessed for demographics, results of coronary angiography, and nuclear stress testing.

The clinical coronary risk factors present in an individual were used to assess the predictive value of risk factors to diagnose CAD. The risk factors that were assessed were age >45 years in men or >55 years in women, diabetes mellitus, history of hypertension, hyperlipidemia, cigarette smoking, and family history of CAD.

Coronary artery stenosis of >50% involving any epicardial vessel was defined as significant CAD. Severe CAD was defined as a stenosis of >70% involving any of the epicardial coronary vessels. Radionuclide stress test results were defined as positive if they showed the presence of ischemia, irrespective of size (small, medium, or large), severity (mild, moderate, or severe), or reversibility.

Table 1
Baseline patient characteristics (n = 414)

Characteristic	Value
Men	248 (60%)
Age at catheterization (yrs)	60 ± 7.6
Hypertension	201 (48%)
Diabetes mellitus	234 (56%)
Dyslipidemia*	71 (17%)
Family history of CAD†	49 (12%)
Smoking history	167 (40%)
Cause of liver disease	
Viral	162 (39%)
Alcohol	83 (20%)
Alcohol + viral	29 (7%)
Nonalcoholic steatohepatitis	52 (12%)
Primary biliary cirrhosis	11 (3%)
Autoimmune	11 (3%)
Others	24 (6%)
Idiopathic	42 (10%)
Dialysis	92 (22%)
Model for End-Stage Liver Disease (MELD)	21 ± 10

Data are expressed as mean ± SD or as number (percentage).
* Medical record of dyslipidemia or treated with a lipid-lowering drug.
† CAD before the age of 55 years in men and 65 years in women in a direct blood relative.

Continuous variables are expressed as mean ± SD and were compared using Student's unpaired *t* tests. Discrete variables are expressed as percentages and were compared using chi-square analysis. Statistical analysis was performed using SPSS version 20 (SPSS, Inc., Chicago, Illinois). A p value <0.05 was considered statistically significant. Classification and regression tree analysis was used to

Table 2
Predictive value of adenosine single-photon emission computed tomography

Adenosine Myocardial Perfusion Scan	Coronary Angiography		
	Severe CAD (>70% stenosis)	No CAD (<70% stenosis)	
Ischemia	TP = 20	FP = 46	PPV = 30%
No ischemia	FN = 12	TN = 215	NPV = 95%
	Sensitivity = 62%	Specificity = 82%	
	CAD (>50% stenosis)	No CAD (<50% stenosis)	
Ischemia	TP = 21	FP = 45	PPV = 32%
No ischemia	FN = 18	TN = 209	NPV = 92%
	Sensitivity = 54%	Specificity = 82%	

FN = false negative; FP = false positive; NPV = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive.

Table 3
Predictive value of regadenoson single-photon emission computed tomography

Regadenoson Myocardial Perfusion Scan	Coronary Angiography		
	Severe CAD (>70% stenosis)	No CAD (<70% stenosis)	
Ischemia	TP = 6	FP = 20	PPV = 23%
No ischemia	FN = 11	TN = 143	NPV = 93%
	Sensitivity = 35%	Specificity = 88%	
	CAD (>50% stenosis)	No CAD (<50% stenosis)	
Ischemia	TP = 7	FP = 19	PPV = 27%
No ischemia	FN = 13	TN = 141	NPV = 91%
	Sensitivity = 35%	Specificity = 88%	

FN = false negative; FP = false positive; NPV = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive.

obtain the optimal predictor for CAD for the continuous variable of age on the basis of gender in our patient population. Logistic regression was performed to evaluate the effect of each of the risk factors for predicting CAD, and the regression coefficients were used to determine a score. Using the presence of a risk factor as a value of 1 and the absence of a risk factor as a value of 0, a score was assigned to each case, which gave a minimum score of 0 and a maximum score of 3.5. The sensitivity and specificity of the risk factors as a predictor of CAD on angiography were calculated at different cut-off values of the score. The sensitivity and specificity results for scoring the risk factors were compared with the matched sensitivity and specificity of SPECT studies using McNemar's test.

Results

Baseline patient characteristics are listed in Table 1. Of the 414 patients in the analysis who underwent myocardial perfusion scans and coronary angiography, 248 (60%) were men, 201 (48%) had hypertension, 234 (56%) had diabetes, 71 (17%) had hyperlipidemia, and 92 (22%) were on dialysis. The average age at the time of angiography was 60 ± 7.6 years, with an average Model for End-Stage Liver Disease score of 21 ± 10. There were in total 473 radionuclide scans. Of these, 293 (62%) used adenosine as the vasodilating agent, and 180 (38%) used regadenoson. There were 38 patients who underwent scans after revascularization procedures (percutaneous coronary intervention) to assess the status of the coronary arteries and stents. The postprocedural angiogram was used in these cases to compare to the radionuclide stress test results. CAD (>50% stenosis) was present in 17% of the patient cohort (n = 70), while 13% of patients (n = 55) had severe CAD (>70% stenosis).

There were 293 adenosine scans (62%) (Table 2). The sensitivity of adenosine perfusion scans for diagnosing severe CAD was 62%, and the specificity was 82%. Results for CAD with diameter stenosis >50% were also similar (sensitivity 54%, specificity 82%). The negative predictive value of adenosine scans for ruling out severe CAD was 95% and for CAD of > 50% stenosis was 92%. The positive predictive value of adenosine scans for diagnosing severe CAD was 30% and for CAD of >50% stenosis was 32%.

There were 180 regadenoson scans (38%). Results of the regadenoson scans are listed in Table 3. The sensitivity of the regadenoson perfusion scan was 35% and the specificity 88% for predicting severe CAD. The results did not change when the cutoff for CAD was lowered to stenosis of >50% (sensitivity 35%, specificity 88%). Regadenoson scans performed well in terms of negative predictive value (93% for severe CAD and 91% for CAD of >50% stenosis), but the positive predictive value for diagnosing CAD was low (23% for severe CAD and 27% for CAD of >50% stenosis). Pearson's chi-square value for adenosine versus regadenoson was 0.80 (p = 0.37), suggesting no significant association between the 2 tests. The chi-square value for the sensitivity of the 2 tests was 0.6 (p = 0.44), and the chi-square value for the specificity of the 2 tests was 0.46 (p = 0.50), again suggesting no significant association between the 2 test results.

Table 4
Risk factor logistic regression

Variable	Coefficient (B)	p Value	Odds Ratio (exp[B])
Age >60 yrs	0.6	0.047	1.8
Hypertension	0.4	0.12	1.6
Hyperlipidemia	1.3	0.0001	3.6
Diabetes mellitus	0.3	0.38	1.3
Cigarette smoking	0.1	0.67	1.1
Family history of CAD	0.8	0.03	2.2

By linear regression analysis, the cut-off age of CAD for men was 59.4 years and for women was 63.1 years, so the cutoff for both genders was chosen to be ≥60 years. Standardized coefficient (B value) results for the risk factors are listed in Table 4. The generated score was equal to (age >60 years × 0.6) + (hypertension × 0.4) + (hyperlipidemia × 1.3) + (diabetes mellitus × 0.3) + (history of cigarette smoking × 0.1) + (family history of CAD × 0.8). Using the presence of a risk factor as a value of 1 and the

absence of a risk factor as a value of 0, a score was assigned to each case, which gave a minimum score of 0 and a maximum score of 3.5. From the score generated, the sensitivity and specificity of risk factors was calculated at different cutoffs of scores. The cut-off score of 1.4 had sensitivity of 50% and specificity of 81%. Using McNemar's test, the cut-off result at a score of 1.4 was compared to the adenosine scan results (sensitivity 54%, specificity 82%). McNemar's p value for sensitivity was 0.48 and for specificity was 1.00, demonstrating no statistical difference between the adenosine SPECT scan and risk factor analysis. The cut-off score of 2.0 had sensitivity of 36% and specificity of 90%, which was compared to the regadenoson scan results (sensitivity 35%, specificity 88%). McNemar's p value for sensitivity was 0.77 and for specificity was 1.00, again demonstrating no statistical difference between the regadenoson SPECT scan and risk factor analysis.

Discussion

Adenosine and regadenoson are both coronary vasodilating agents with very limited effects on systemic vascular resistance. Adenosine is a nonselective adenosine A_2 receptor agonist, while regadenoson is a selective adenosine A_{2A} receptor agonist, and both induce coronary vasodilation. Regadenoson, approved by the United States Food and Drug Administration in April 2008, is increasingly used as a stress agent of choice because of its ease of administration as a bolus, weight-unadjusted dose, fast onset and short duration of action, sufficient hyperemic response, and comparable efficacy to adenosine but with fewer side effects.[15,16] The safety of regadenoson in patients with liver failure has been addressed in 1 study,[17] but no previous study has described the predictive value of regadenoson in patients with liver failure. Studies with adenosine SPECT imaging in patients with ESLD have also been limited, and results have been inconsistent. Davidson et al[10] reported sensitivity of 37% and specificity of 63% for a group of 83 patients. Aydinalp et al[11] reported an unusually high sensitivity of 100% with specificity of 61% and negative predictive value of 100% in 93 candidates for liver transplantation. Our study population is 4 times as large as these other studies, and our findings are consistent with the report of poor sensitivity of these pharmacologic radionuclide imaging studies. Our study also shows that using the cut-off criteria for CAD as either >50% diameter stenosis or >70% diameter stenosis did not change the predictive accuracy of SPECT scans. The low sensitivity of pharmacologic stress tests in patients with liver failure may be due to these patients' decreased coronary vascular resistance, which could minimize additional vasodilation in response to pharmacologic stress agents.

Selecting an appropriate noninvasive stress test in patients with liver failure remains a challenge. Most of the patients cannot exercise because of their advanced liver disease. Results with dobutamine stress echocardiography have shown poor sensitivity and low negative predictive value, partially because of an inability to reach target heart rate.[2,12,13] Most of these patients are on β blockers to decrease portal hypertension and prevent esophageal bleeding. Ideally, a noninvasive test should be highly sensitive to diagnose CAD in potential transplantation patients, considering the perioperative cardiovascular complication risks involved with the surgery. Our data corroborate the low sensitivity and low positive predictive value for SPECT imaging tests in patients with ESLD. Patients with low pretest probability of CAD may obtain accurate results. All abnormal SPECT results, as well as those at risk for high pretest probability of CAD, should be confirmed by coronary angiography. A clinician facing the question of whether to send a patient with ESLD for high-risk liver transplantation surgery needs to know whether CAD is present with a higher degree of accuracy than is achieved with current radionuclide pharmacologic stress imaging. In a single study, coronary multidetector computed tomographic angiography emerged as an attractive alternative to SPECT studies, but the results were not compared to those obtained with conventional angiography.[18] Tachycardia associated with ESLD is currently an impediment to obtaining accurate computed tomographic angiograms in these patients. With faster computed tomographic imaging, this problem may be overcome in the future.

Adenosine and regadenoson had low sensitivity to detect CAD in this patient population, with no statistical difference between the 2 tests (chi-square = 0.804, p = 0.37). In addition, the results of a standard risk factor analysis were no different from the results of either of the 2 SPECT scans, raising the question of the utility of performing SPECT scans in patients with ESLD. Also, the evaluating physician often disregarded negative SPECT results and ordered angiography to rule out CAD, which demonstrates a lack of confidence in the results of these tests. In contrast, in select groups of patients who are being evaluated for ischemic heart disease, myocardial perfusion imaging is reported to have higher sensitivity of 84% and specificity of 77% for identifying patients with 50% diameter stenosis.[19] Fractional flow reserve is more accurate than coronary angiography to assess the physiologic significance of a stenosis, and in the current era, fractional flow reserve is the gold standard for diagnosing the significance of CAD.[20,21]

Our results of 473 radionuclide pharmaceutical stress tests in patients with ESLD suggest that a standard risk factor assessment provides results that are equivalent to those of radionuclide imaging studies. This risk stratification can be obtained without the additional radiation and expense to patients of radionuclide imaging.

Disclosures

The authors have no conflicts of interest to disclose.

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