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

Suchit Bhutani, MD\textsuperscript{a}, Jonathan Tobis, MD\textsuperscript{a,*}, Rubine Gevorgyan, MD\textsuperscript{a}, Arjun Sinha, MD\textsuperscript{a}, William Suh, MD\textsuperscript{a}, Henry M. Honda, MD\textsuperscript{b}, Gabriel Vorobiof, MD\textsuperscript{a}, René R.S. Packard, MD\textsuperscript{a}, Randolph Steadman, MD\textsuperscript{b}, Christopher Wray, MD\textsuperscript{b}, Ronald Busuttil, MD\textsuperscript{c}, and Chi-hong Tseng, PhD\textsuperscript{d}

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. © 2013 Elsevier Inc. All rights reserved. (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%\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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
Figure 1. Myocardial perfusion imaging was performed per standard protocols. 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
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 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.

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

| 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                 |
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 A2 receptor agonist, while regadenoson is a selective adenosine A2A 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 al10 reported sensitivity of 37% and specificity of 63% for a group of 83 patients. Aydinalp et al11 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 results 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 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 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.

1. Carey WD, Dumot JA, Pimentel RR, Barnes DS, Hobbs RE, Henderson JM, Vogt DP, Mayes JT, Westveer MK, Easley KA. The prevalence of coronary artery disease in liver transplant candidates over age 50. *Transplantation* 1995;59:859–864.
2. Plotkin JS, Benitez RM, Kuo PC, Njoku MJ, Ridge LA, Lim JW, Howell CD, Laurin JM, Johnson LB. Dobutamine stress echocardiography for preoperative cardiac risk stratification in patients undergoing orthotopic liver transplantation. *Liver Transpl Surg* 1998;4: 253–257.
3. Tiukinhoy-Laing SD, Rossi JS, Bayram M, De Luca L, Gafoor S, Bliel A, Flamm S, Davidson CJ, Gheorghiade M. Cardiac hemodynamic and coronary angiographic characteristics of patients being evaluated for liver transplantation. *Am J Cardiol* 2006;98:178–181.
4. Plotkin JS, Scott VL, Pinna A, Dobisch BP, De Wolf AM, Kang Y. Morbidity and mortality in patients with coronary artery disease undergoing orthotopic liver transplantation. *Liver Transp Surg* 1996;2:426–430.

5. Safadi A, Homsi M, Maskoun W, Lane KA, Singh I, Sawada SG, Mahenthiran J. Perioperative risk predictors of cardiac outcomes in patients undergoing liver transplantation surgery. *Circulation* 2009;120:1189–1194.

6. Diedrich DA, Findlay JY, Harrison BA, Rosen CB. Influence of coronary artery disease on outcomes after liver transplantation. *Transplant Proc* 2008;40:3554–3557.

7. Wray C, Scovotti JC, Tobis J, Niemann CU, Planinsic R, Walia A, Findlay J, Wagener G, Cywinski JB, Markovic D, Hughes C, Humar A, Olmos A, Sierra R, Busuttil R, Steadman RH. Liver transplantation outcome in patients with angiographically proven coronary artery disease: a multi-institutional study. *Am J Transplant* 2013;13:184–191.

8. Eagle KA, Berger PB, Calkins H, Chairman BR, Ewy GA, Fleischmann KE, Fleisher LA, Froehlich JB, Gubberg RJ, Leppo JA, Ryan T, Schlant RC, Winters WL Jr, Gibbons RJ, Antman EM, Aplert JS, Faxon DP, Fuster V, Gheorghiade M, Hiratzka LF, Russell RO, Smith SC Jr. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. ACC/AHA guideline on perioperative risk assessment of noncardiac surgery. *Circulation* 2002;105:1257–1267.

9. Tripodi A, Mannucci PM. The coagulopathy of chronic liver disease. *N Engl J Med* 2002;346:1523–1528.

10. Davidson CJ, Gheorghiade M, Flaherty JD, Elliot MD, Reddy SP, Wang NC, Sundaram SA, Flamm SL, Blei AT, Abecassis MI, Bonow RO. Predictive value of stress myocardial perfusion imaging in liver transplant candidates. *Am J Cardiol* 2002;89:359–360.

11. Aydinalp A, Bal U, Atar I, Ertan C, Aktas A, Yildirir A, Ozin B, Muddersoglu H, Haberal M. Value of stress myocardial perfusion scanning in diagnosing CAD in liver transplantation candidates. *Transplant Proc* 2009;41:3757–3760.

12. Harinstein ME, Flaherty JD, Ansari AH, Robin J, Davidson CJ, Rossi JS, Flamm SL, Blei AT, Bonow RO, Abecassis M, Gheorghiade M. Predictive value of dobutamine stress echocardiography for coronary artery disease detection in liver transplant candidates. *Am J Transp* 2008;8:1523–1528.

13. Williams K, Lewis JF, Davis G, Geiser EA. Dobutamine stress echocardiography in patients undergoing liver transplantation evaluation. *Transplantation* 2000;69:2534–2536.

14. Henzlova MJ, Cerqueira MD, Taillefer R, Mahmarian JJ, Yao S-S. ASNC imaging guidelines for nuclear cardiology procedures: stress protocols and tracers. *J Nuc Card* 2009;16:331.

15. Iskandrian AE, Bateman TM, Belardinelli L, Blackburn B, Cerqueira MD, Hendel RC, Lieu H, Mahmarian JJ, Olnsted A, Underwood SR, Vitola J, Wang W. Adenosine versus regadenoson comparative evaluation in myocardial perfusion imaging: results of the ADVANCE phase 3 multicenter international trial. *J Nucl Cardiol* 2007;14:645–658.

16. Cerqueira MD, Nguyen P, Staehr P, Underwood SR, Iskandrian AE. Effects of age, gender, obesity, and diabetes on the efficacy and safety of the selective A2A agonist regadenoson versus adenosine in myocardial perfusion imaging: integrated ADVANCE-MPI trial results. *J Am Coll Cardiol Img* 2008;1:307–316.

17. Aljaroudi W, Iqbal F, Koneru J, Bhambhvani P, Heo J, Iskandrian AE. Safety of regadenoson in patients with end-stage liver disease. *J of Nuc Card* 2011;18:90–95.

18. Keeling NA, Flaherty JD, Davarpanah AH, Ambrosy A, Farrelly CT, Harinstein ME, Flamm SL, Abecassis MI, Skaro AI, Carr JC, Gheorghiade M. Coronary multidetector computed angiography to evaluate coronary artery disease in liver transplant candidates: methods, feasibility and initial experience. *J Cardiovasc Med* 2011;12:460–468.

19. Schinkel AF, Bax JJ, Geleijnse ML, Boersma E, Elhendy A, Roelantd JRTC, Poldermans D. Noninvasive evaluation of ischemic heart disease: myocardial perfusion imaging or stress echocardiography? *Eur Heart J* 2003;24:789–800.

20. Ragosta M, Bishop AH, Lipson LC, Watson DD, Gimple LW, Sarembau JJ, Powers ER. Comparison between angiographic and fractional flow reserve versus single-photon emission computed tomographic myocardial perfusion imaging for determining lesion significance in patients with multivessel coronary disease. *Am J Cardiol* 2007;99:896–902.

21. Melikian N, De Bondt P, Tonino P, De Winter O, Wyffels E, Bartunek J, Heyndrickx GR, Fearon WF, Pijls NHJ, Wijns W, De Bruyne B. Fractional flow reserve and myocardial perfusion imaging in patients with angiographic multivessel coronary artery disease. *J Am Coll Cardiol Intv* 2010;3:307–314.