Accuracy of Myocardial Perfusion Imaging to Diagnose Coronary Artery Disease in Patients Undergoing Liver Transplantation

Alba AC*, Doumouras BS¹, Mocironita AG¹, Renner EL² and Delgado DH³

Abstract

Background: Assessing cardiac risk in patients with advanced liver disease is complex due to difficulties in evaluating patient’s functional capacity. The purpose of this study was to evaluate the accuracy of Myocardial Perfusion Imaging (MPI) to identify Coronary Artery Disease (CAD) in this group of patients.

Methods: In this retrospective study, we included 115 advanced-liver-disease patients undergoing MPI and coronary catheterization. Patient’s demographic characteristics, cardiovascular risk factors and type of liver disease were assessed. We analyzed sensitivity, specificity and likelihood ratio of MPI to detect CAD (≥50% stenosis). The test results were divided among three possible results: normal (no perfusion defects), only 1-area defect and >1-area defect.

Results: Forty-three patients had abnormal MPI (defined as ≥1 areas of ischemia). Thirty-eight had CAD. The sensitivity and specificity of 1-area defect to identify CAD was 66% and 52% respectively and changed to 57% and 96% respectively when >1-area defect was used. The likelihood ratio was 0.77 for a normal test result, 1.6 in patients with 1-area defect and 23 in patients with >1-area defect. These results illustrate poor test properties for normal or mildly positive test results and high test properties for >1-area of ischemia.

Conclusions: Cardiovascular disease is a common cause of death in patients with advanced liver disease pre- and post-transplantation. Myocardial perfusion imaging is a useful test to detect CAD. However, it does not add diagnostic value in the presence of normal or mildly positive results.

Keywords

Liver transplantation; Myocardial perfusion test; Sensitivity; Specificity

Introduction

Cardiovascular disease is a common cause of early and late morbidity and mortality in patients undergoing liver transplantation [1-3]. In fact, it remains as one of the leading causes of non-graft-related death in the long-term, reaching a 20% mortality rate for those patients who survive the third year post-transplantation. In addition, liver-transplant recipients with known Coronary Artery Disease (CAD) have a 5-fold increased mortality risk than those without CAD [4]. Substantial efforts and changes have been made to decrease the impact of CAD in patients undergoing liver transplantation.

The detection and appropriate treatment of CAD in patients who are potential candidates for a liver transplantation are both necessary to decrease the perioperative transplant risk and long-term mortality [4]. While exercise ECG remains the most widely used noninvasive stress test for the detection of CAD [5], cardiac risk assessment using this modality in patients with advanced liver disease may be complex due to a patient’s poor functional capacity. This situation leads to more extensive preoperative evaluation, including imaging stress tests and coronary catheterization. In liver transplant candidates, a common noninvasive test employed to assess CAD is Dobutamine Stress Echocardiography (DSE). However, its effectiveness has been called into question. In one study of 105 patients that underwent both DSE and coronary angiography prior to orthotopic liver transplantation (OLT), DSE was found to have very low sensitivity of 13%, though retaining a high specificity at 85%. Furthermore, there was a low Positive Predictive Value (PPV) at 22% and negative predictive value (NPV) of 75%. These unfavourable results may be secondary to the inability of patients to achieve target heart rate [6].

A meta-analysis on studies analyzing pharmacological Myocardial Perfusion Imaging (MPI) for detection of CAD (50% or more stenosis) have reported a sensitivity from 82% to 90% and a specificity from 65 to 75%, depending on the type of pharmacological stress used [7,8]. However, the sensitivity, specificity, and test properties of MPI may not be equal in different populations. Therefore, the objective of this study was to evaluate the accuracy of MPI, to identify CAD in advanced liver disease patients prior to liver transplantation.

Patients and Methods

Patient population

From January 2003 to December 2008, a total of 344 pre-liver transplant patients were evaluated to assess cardiovascular risk at a single institution. Of those, 265 patients who underwent an MPI were retrospectively included in this study. Of this group, only 115 patients underwent a coronary catheterization. Patients with isolated coronary angiogram were excluded (6 patients). Appropriate institutional review board approvals were obtained to review clinical data obtained from charts and clinic visits.

Stress tests

Results from MPI test were obtained from chart review. MPI test was performed using 99mTc-sestamibi in 90% of the patients; 201Thallium was the isotope used in 10% of the patients. The sensitivity and specificity of 99mTc-sestamibi and 201Thallium testing have been shown to be similar [9,10]. Dipyridamole was the stress modality used in all the patients; except in 12 patients who were able to exercise and an exercise stress was induced. MPI was obtained using tomographic acquisition at both stress and rest. Normal studies

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were those without stress perfusion defects or minimal perfusion defects easily attributable to attenuation (e.g. breast attenuation). A test was considered to reflect ischemia if there was 1 or more stress-induced defect reversible at rest. The test results were divided among three possible results: normal (no perfusion defects), only 1-area defect, and >1-area defect. Of the 265 patients who underwent MPI, only 115 were referred for coronary angiogram. This may lead to “verification bias” or “work-up bias”, in which the decision of performing coronary angiography may have been influenced by the results of the MPI increasing the chance of undergoing a coronary angiogram in patients with abnormal test results. This bias can falsely increase sensitivity and decrease specificity [11]. This was taken into consideration in the analysis of this study.

Coronary angiography

The decision to refer patients to coronary angiography was made by a cardiologist based on the presence of cardiovascular risk factors, symptoms suspicious of myocardial ischemia and results of the MPI. Patients who were deemed as low cardiovascular risk (absence of cardiovascular symptoms, presence of less than two cardiovascular risk factors and a putative positive MPI test result) were not referred to coronary angiography. The degree of coronary stenosis was visually assessed by an experienced interventional cardiologist. The presence of CAD was defined as ≥ 50% diameter narrowing in any of the major coronary arteries or their major branches.

Variables

Patient’s baseline characteristics, including demographic, type of liver disease, cardiovascular risk factors, Left Ventricular (LV) ejection fraction and LV mass (assessed by echocardiogram), laboratory values, and medication at the time of cardiac assessment, were analyzed.

Outcomes

Outcomes evaluated were cardiovascular complications, including Acute Coronary Syndrome (ACS) and new-onset heart failure, need for myocardial revascularization and cardiovascular death, and liver transplantation. Death was considered as cardiovascular death when it was due to myocardial infarction, sudden death or acute decompensated heart failure.

Statistical analysis

Continuous variables are presented as mean value ± standard deviation (SD) and categorical data expressed as percentage. We conducted univariable analysis to compare the characteristics among patients with normal test result, 1 area-defect and >1-area defect. We used one-way ANOVA for continuous variables and chi-square analysis for categorical variables to determine statistical significance. A p-value of ≤ 0.05 was considered statistically significant.

We analyzed sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and likelihood ratio (LR) of MPI to detect CAD. The positive LR provides a direct estimate of how much the odds of a disease (CAD) increase when a test is positive and was calculated as sensitivity/(1-specificity). The negative LR expresses how much the odds of a disease (CAD) decrease when a test is negative and was calculated as (1-sensitivity)/specificity. We converted odds to probability using the equation: Odds=probability/(1–probability).

In order to correct for verification bias, we calculated corrected sensitivity and specificity. The corrected sensitivity was calculated as 100×([PPV×PA]/[PA×(1–PPV)+(1–PA)×(1–NPV)]), where PA is the proportion of abnormal MPI among the population referred and non-referred for cardiac catheterization. The corrected specificity was 100×[1–[PA×(1–PPV)]/[PA×(1–PPV)+(1–PA)×NPV]) [12]. The statistical analysis was performed with the use of SPSS 17.1 and Microsoft Office Excel 2007. We expressed measures of uncertainty as 95% confidence intervals (CI) and calculated them using online software by Richard Lowry [13].

In order to assess the applicability of these results, we performed a sensitivity analysis of the corrected sensitivity and specificity for different pre-test probabilities and proportion of abnormal test results in the population of interest.

Results

Of the 265 study patients, 115 (43%) underwent a coronary angiography and 150 did not. Of the 115 patients, 43 (37%) had an abnormal MPI with at least 1-area defect and 19 (17%) patients had a >1-area defect. Demographic data for the 115 patients who underwent coronary angiography are presented in table 1. The mean age was 56 years (minimum age of 35 and maximum of 68 years)

Table 1: Baseline characteristics.

| Variable | Patients (n=115) | Mean ± SD / n (%)
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Age</td>
<td>56 ± 10</td>
<td></td>
</tr>
<tr>
<td>Male gender</td>
<td>93 (81)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28 ± 6</td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>11 (10)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>34 (30)</td>
<td></td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>31 (27)</td>
<td></td>
</tr>
<tr>
<td>NASH</td>
<td>12 (10)</td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>28 (24)</td>
<td></td>
</tr>
<tr>
<td>MELD score</td>
<td>13 ± 7</td>
<td></td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.2 ± 0.8</td>
<td></td>
</tr>
<tr>
<td>CV risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>63 (55)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>69 (61)</td>
<td></td>
</tr>
<tr>
<td>Insulin use*</td>
<td>45 (68)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>29 (27)</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>35 (32)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>21 (19)</td>
<td></td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>44 (42)</td>
<td></td>
</tr>
<tr>
<td>Previous history of CAD</td>
<td>28 (24)</td>
<td></td>
</tr>
<tr>
<td>Echocardiogram parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>84 ± 10</td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction &lt;50%</td>
<td>5 (5)</td>
<td></td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>93 ± 25</td>
<td></td>
</tr>
<tr>
<td>LV mass index &gt;130 g/m²</td>
<td>5 (5)</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>75 (65)</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>16 (14)</td>
<td></td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>33 (29)</td>
<td></td>
</tr>
</tbody>
</table>

BMI: Body mass index; NASH: Non-alcoholic steato-hepatitis; MELD: Model for end-stage liver disease; CV: Cardiovascular; CAD: Coronary artery disease; LV: Left ventricular; ACE: Angiotensin-converting enzyme.

* Only considering diabetic patients.


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and 93 (81%) patients were male. The main causes of liver disease were Hepatitis C (30%) and alcoholic cirrhosis (27%). Among cardiovascular risk factors, more than a half of the population had diabetes and hypertension; obesity and dyslipidemia were present in around 30% of the patients. Left ventricular ejection fraction was preserved in 95% of the patients.

Of the 115 patients who underwent catheterization, 38 (33%) patients had angiographic evidence of CAD (Table 2). Therefore, the observed sensitivity for at least 1-area defect was 66% (25/38) and the observed specificity was 52% (40/77) (Table 3), the PPV was 40% (25/62) and the NPV was 75% (40/53). Of the 150 patients not referred to coronary angiogram, only 32 patients (21%) had an abnormal test result (26 patients had a 1-area defect and 6 patients had a >1-area defect) (Figure 1). Thus the proportion of abnormal test results (PA) was 26% (43+26/265) for at least 1-area defect and 9% (19+6/265) for >1-area defect. Therefore, after correction for verification bias, the sensitivity was 44% and specificity was 72%. The sensitivity for a >1-area defect was 58% (22/38), the specificity was 96% (74/77), the PPV was 88% (22/25), and the NPV was 82% (74/90). The corrected sensitivity was 33% and the corrected specificity was 99%. Based on these results, the positive LR to detect CAD when the test showed at least 1-area defect was 1.6 and for >1-area defect was 23. The negative LR was 0.77.

Table 4 shows the clinical characteristics of patients according to the results of the MPI. There were not significant differences among groups.

**Sensitivity analysis**

The positive LR was low in patients with at least 1-area defect (LR=1.6) and much higher in patients with >1-area defect (LR=23). Based on these results, table 5 and figure 2 shows the results of the analysis of the post-test probability according to the pre-test probability and test results to diagnose CAD. In general, the post-test probability does not change substantially if patients have a normal test result or a 1-area defect test result. For example, in a hypothetical patient with a pre-test probability of having CAD of 50%, a normal test result or a 1-area defect test result. For example, in a hypothetical patient with a pre-test probability of having CAD of 50%, a normal test result decreases the probability to 44% and a test result with a 1-area defect increases the probability to 61%. However, in patients with >1-area defect testing results the post-test probability of having CAD increases considerably (a pre-test probability of 50% is increased to 96%).

**Outcomes**

In the group of patients with CAD (38 patients), 8 patients were not listed for liver transplantation due to high cardiovascular risk; 14 patients underwent myocardial revascularization (13 patients angioplasty and 1 patient bypass surgery), of those 3 patients died due to cardiovascular causes (2 patients due to sudden death and one with decompensated heart failure) prior to transplant. Eleven patients underwent liver transplantation. Post-transplant, four patients had an ACS; three of them required coronary angioplasty. In addition, three patients died due to cardiovascular cause (2 patients due to...
Table 5: Pre and post-test probability of moderate and severe CAD according to the likelihood ratio.

<table>
<thead>
<tr>
<th>Pre-test probability (%)</th>
<th>MPI result (LR)</th>
<th>Post-test probability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>70</td>
<td>Normal (0.77)</td>
<td>64</td>
</tr>
<tr>
<td>70</td>
<td>1-area defect (1.6)</td>
<td>79</td>
</tr>
<tr>
<td>70</td>
<td>&gt;1-area defect (23)</td>
<td>98</td>
</tr>
<tr>
<td>50</td>
<td>Normal (0.77)</td>
<td>44</td>
</tr>
<tr>
<td>50</td>
<td>1-area defect (1.6)</td>
<td>61</td>
</tr>
<tr>
<td>50</td>
<td>&gt;1-area defect (23)</td>
<td>96</td>
</tr>
<tr>
<td>20</td>
<td>Normal (0.77)</td>
<td>16</td>
</tr>
<tr>
<td>20</td>
<td>1-area defect (1.6)</td>
<td>29</td>
</tr>
<tr>
<td>20</td>
<td>&gt;1-area defect (23)</td>
<td>85</td>
</tr>
</tbody>
</table>

Figure 2: Pre- and post-test probability of coronary artery disease according to test result of myocardial perfusion imaging. The dotted line represents a test without predictive value. Normal and 1-area defect test results are close to that line showing poor predictive value (small change in post-test probability); however, >1-area defect result shows a high predictive value demonstrating an important increase in post-test probability.

Discussion

There exists controversy in terms of the most appropriate noninvasive screening method for CAD in OLT candidates as there is a lack of established guidelines and inconclusive evidence [14–21]. The aim of the present study was to evaluate the accuracy of MPI to identify CAD in patients with advanced liver disease as part of the transplantation assessment. Specifically, we evaluated the sensitivity and specificity of myocardial perfusion imaging versus coronary angiography. Our main finding was that in contrast to previous studies, there is a possible role for MPI in patients who present with a greater than one area defect. However, a negative or mildly positive result (1-area defect) does not add any diagnostic value making it necessary to further pursue other tests (both invasive and non-invasive).

To our knowledge, there are only two previous studies, Davidson et al. [16] and Ayndinalp et al. [18], in which the sensitivity and specificity of myocardial perfusion imaging in OLT candidates were evaluated. These studies included 83 and 93 liver transplant candidates respectively. In both studies, all patients underwent MPI and coronary angiography regardless of the MPI results. These authors defined clinically relevant CAD on coronary angiography as a stenosis of 70% or greater.

One of the main differences between studies is the definition of perfusion abnormalities. Davidson et al. [16] considered all SPECT scans defects as positive regardless of size, severity, or reversibility, reporting a sensitivity of 37% and a specificity of 63%. Ayndinalp et al. [18] considered only reversible perfusion defects to be positive and reported a sensitivity of 100% and a specificity of 61%. In our study, we analyzed results by dividing them into three categories: normal (no perfusion defect), 1-area reversible defect, or >1-area reversible defect. The advantage of this method is that we were able to deduce the sensitivity and specificity of different extents of ischemic area. The results did in fact indicate that in cases of more extensive CAD (i.e. greater than 1-area defect), MPI is a valuable screening tool.

Our study shows that an MPI result of >1-area defect significantly increases the probability of having underlying CAD while a normal value does not provide additional diagnostic value. A test result of >1-area defect leads to a sensitivity of 33% and a specificity of 99%. It has been suggested that the low sensitivity is likely a result of the decreased arterial vascular resistance in OLT candidates. Due to this, coronary arteries would not be able to adequately respond to vasodilating agents [16].

While many past studies suggest that MPI may not be useful for screening [14,16,18,19], our study proposes that there is in fact a role in a select group of patients. This may help physicians to indicate more therapies in order to adequately treat these patients and maximize their post-transplant outcomes. However, a normal test or a test showing 1-area defect does not add any diagnostic value to this population. This fact has led physicians to do other non-invasive tests, such as stress echocardiogram or directly indicate a coronary angiography based on clinical judgment. However, it is important to highlight that our study did not identify any significant clinical differences among patients with different test results.

The relatively low specificity (71%) of test results of 1-area defect to detect CAD may be due to the presence of specific conditions in patients with advanced liver disease that mimic the results of an abnormal MPI of patients with CAD. These conditions are related to the high proportion of artifacts in the inferior wall principally due to the higher diaphragm position in some patients with advanced liver disease that can overlap the inferior wall and provoke attenuation artifacts. In addition, liver enlargement may act as a "hot" extracardiac structure decreasing relatively or absolutely the amount of counts from the heart during the calculation of the MPI images [22,23].

It has been proposed that the LR may be used to describe the properties of a particular test. The reason is because the LR is easier to apply to clinical practice and is not influenced by the number of the patients included in the study [24,25]. Based on the results of our study, in patients with CAD, the probability of having a positive MPI test result with 1-area defect was 1.6 times higher than in patients without CAD. Conversely, in patients with CAD, the probability of having a positive test result with >1-area defect was 23 times higher than in patients without this disease, thereby increasing considerably the post-test probability. On the other hand, in patients with CAD, a

sudden death and one due to ACS). In the group of patients without CAD (77 patients), all patients were listed for transplant and 27 underwent liver transplant. Post-transplant, five developed an ACS treated medically. Only one patient died due to cardiovascular cause (new-onset heart failure).


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normal MPI was 1.3 (1/0.77) less frequent than in patients without CAD. In other words, the presence of a normal or 1-area defect in a MPI test does not substantially change the probability of having CAD. However, MPI with >1-area defect result has an important impact on the post-test probability and helps in the decision to follow a more aggressive medical management approach, including implementation of treatment for CAD and indication of coronary angiogram.

Other non-invasive tests have been evaluated in patients undergoing liver transplantation. For example, Umphrey et al. [26] studied 157 liver-recipients patients who had a DSE prior to transplantation. They reported that the maximum achieved heart (<85%) and peak rate pressure product (<16500) during the test were associated with higher risk of cardiovascular events post-transplant. However, as previously mentioned, the utility of DSE is inconclusive. In addition, McAvoy et al. [27] reported that coronary artery calcification score is a marker of occult CAD in patients with end-stage liver disease and correlates positively with other cardiac factors, including age, male sex, family history of cardiovascular disease, fasting glucose, systolic and diastolic blood pressure, number of coronary vessels involved, and components of the metabolic syndrome. However, results of the properties of these modalities to diagnose CAD in liver transplant candidates have not been reported. The indication of these tests may help to guide clinical practice in those patients with doubtful MPI results before undergoing coronary angiogram.

Though previous studies have failed to indicate a role for MPI in the detection of CAD in advanced liver disease patients, a recent study by Oprea-Lager et al. [21] has shown some clinical usefulness. They observed that the presence of one or more reversible defects was associated with increased all-cause mortality in the one-year period following liver transplantation. Cardiac mortality was not the sole reason for this as infection was the main cause of death. The described prognostic value or >1-area defect in addition to the high test accuracy to detect such a defect increases the importance and clinical utility of performing an MPI as a screening prognostic tool in candidates for liver transplantation.

Study Limitations

The main limitation of this study was patient selection bias. We only included patients who underwent cardiac catheterization. This factor can influence the MPI's properties due to the exclusion of patients without CAD. Therefore, the result of the MPI may only correspond to patients with higher likelihood of CAD. In addition, the retrospective nature limits the interpretation of the results; mainly the blind assessment of coronary angiogram is not warranted. However, this fact would increase the test properties, which is not entirely supported by the findings of this study. Most of subject included in this study had normal left ventricular function; caution should be taken when extrapolating these results to patients with heart failure. Similarly, only 19% of the patients included in this study were female. This under-representation of women limits the generalization of our results. It is well appreciated that the diagnostic accuracy of MPI in women is adversely affected by gender specific factors such as breast attenuation, small left ventricular chamber size, and a high prevalence of single vessel CAD.

Conclusion

Cardiovascular disease is a common cause of morbidity and mortality in patients with advanced liver disease pre and post-transplantation. The present study demonstrated that an MPI is a useful tool in patients with CAD in terms of helping physicians in the cardiovascular assessment of those with advanced liver disease who present with more than one area defect. However, in patients with a negative or mildly positive result, it is necessary to do other non-invasive tests to confirm or discharge the diagnosis of CAD and indicate a coronary angiogram.

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References


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