

Predictive Value of Dobutamine Stress Perfusion Echocardiography in Contemporary End-Stage Liver Disease

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Background—The assessment of cardiac risk in contemporary liver transplantation (LT) has required more sensitive testing for the detection of occult coronary artery disease as well as microvascular and functional cardiac abnormalities. Because dobutamine stress perfusion echocardiography provides an assessment of both regional systolic and diastolic function as well as microvascular perfusion (MVP), we sought to examine its incremental value in this setting.

Methods and Results—We evaluated the predictive value of dobutamine stress perfusion echocardiography in 296 adult patients with end-stage liver disease and preserved systolic function who underwent LT between 2008 and 2014. The primary outcome was cardiovascular death, nonfatal myocardial infarction, and/or sustained ventricular arrhythmias following LT. The main causes of liver failure were hepatitis C (25%) and nonalcoholic fatty liver disease (13%). Abnormal MVP during stress was observed in 18 patients (6%), whereas diastolic dysfunction was present in 109 patients (94 grade 1, 15 grade 2). Half of the patients (7 of 14) referred for angiography with abnormal MVP had significant epicardial disease by angiography, and these patients were revascularized prior to LT. Despite these interventions, the primary outcome still occurred in 9 patients (3%). Patients with abnormal MVP during dobutamine stress perfusion echocardiography had a 7-fold higher risk of a cardiovascular event following LT. Cox proportional hazards modeling examining clinical variables, left ventricular ejection fraction, diastolic function, and stress-induced wall motion abnormalities or MVP defects demonstrated that abnormal MVP was the only independent predictor of the primary outcome ($P=0.004$; hazard ratio 7.7).

Conclusions—Stress MVP assessments are highly predictive of cardiovascular outcome in current LT candidates. (*J Am Heart Assoc.* 2017;6:e005102. DOI: 10.1161/JAHA.116.005102.)

Key Words: coronary artery disease • left ventricular ejection fraction • liver transplantation • microvascular dysfunction

Cardiac changes in patients with end-stage liver disease can lead to abnormal cardiac contractility with electromechanical conduction abnormalities and diastolic and systolic dysfunction.¹ Often the systolic dysfunction is masked as a result of decreased afterload from splanchnic vasodilatation but can be uncovered with exercise or pharmacological stress testing.^{2–4} Liver transplantation (LT) is associated with significant hemodynamic changes that require adequate cardiac reserve. There is an abrupt increase in systemic vascular resistance resulting in increased myocardial oxygen demand.⁵ The goal of the cardiovascular assessment prior to LT is to

evaluate whether the patient can adapt to these intra- and postoperative changes.⁶

In the current era, nonalcoholic fatty liver disease is more commonly being detected and requiring LT.⁷ This particular form of advanced liver disease carries with it a higher risk of underlying coronary artery disease (CAD).⁸ The prevalence of CAD in patients with advanced liver disease may be as high as 7.5% and is associated with significant morbidity and mortality.^{9–12} Furthermore, although a significant proportion of patients may not have significant obstructive epicardial coronary disease, they may have significant endothelial dysfunction and abnormal microvascular function.^{13–15} Inducible microvascular perfusion (MVP) defects during demand stress testing, even in the absence of wall motion (WM) abnormalities, have been associated with an increased risk of morbidity and mortality in patients with suspected CAD.¹⁶

Despite these developments, there are still no class 1 indications of how to appropriately evaluate cardiovascular risk in the patient with advanced liver disease.⁶ Unlike current radionuclide imaging techniques, myocardial contrast intensity during a continuous infusion of commercially available microbubbles is able to simultaneously examine regional WM

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An accompanying Video S1 is available at <http://jaha.ahajournals.org/content/6/2/e005102/DC1/embed/inline-supplementary-material-1.mp4>

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Received November 30, 2016; accepted January 13, 2017.

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and microvascular capillary blood flow at rest and during demand stress.^{17,18} In this context, dobutamine stress perfusion echocardiography (DSPE) has been shown to improve the detection of epicardial disease and to identify patients with abnormal microvascular reserve.¹⁷ Because the use of contrast also improves Doppler signal detection and endocardial border delineation,¹⁹ it can also be utilized to detect other subtle cardiac abnormalities that may be associated with increased risk, such as an abnormal diastolic dysfunction or slight variations in left ventricular systolic function, that may predict outcome. Previous studies in an earlier era of LT suggested that MVP abnormalities detected with DSPE may identify those at risk for cardiac complications, but nonalcoholic fatty liver disease patients were not evaluated, event rates were low, and the effects of ejection fraction and diastolic function were not simultaneously assessed.¹⁸ The aim of this study was to evaluate the prognostic importance of DSPE in adult patients undergoing isolated LT for predicting both cardiovascular and overall clinical outcomes in the current era.

Methods

Patients

This retrospective cohort study was approved by the institutional review board at the University of Nebraska Medical Center (UNMC). Data were collected from the electronic health records and the LT database at UNMC. The requirement for informed consent was waived by our institutional review board. In total, 724 pediatric and adult patients underwent LT at UNMC between January 19, 2008, and June 7, 2014. A total of 508 (70%) received an isolated single-organ LT, and 296 of these adult patients (40%) underwent DSPE to assess baseline systolic and diastolic function as well as perfusion and WM response as part of the initial screening for LT (Figure 1). Demographic data such as age, sex, cardiac risk factors, and race were collected. The Model for End-Stage Liver Disease (MELD) score was used to determine the severity of liver disease using the composite of 3 laboratory variables: serum creatinine, serum bilirubin, and International Normalized Ratio for prothrombin time. If patients had a history of prior CAD (prior percutaneous or surgical revascularization or angiogram demonstrating >50% coronary artery obstruction), this was also recorded. Exclusion criteria included those with left ventricular ejection fraction (LVEF) <40%, age <19 years, or allergy to perflutren contrast.

Dobutamine Stress Perfusion Echocardiography

The contrast agent used for DSPE was the commercially available lipid-encapsulated microbubble Definity (Bristol-

Myers Squibb Medical Imaging). Contrast agents were administered as a continuous 3% intravenous infusion during real-time imaging at a very low mechanical index. The systems were adjusted to achieve the optimal nonlinear signal at a mechanical index of <0.2 and a frame rate of 25 Hz. Time-gain compensation and 2-dimensional gain settings were adjusted as recommended to suppress any signals from tissue prior to contrast injection and remained unchanged throughout the study.¹⁹

In all patients, baseline measurements of systolic and diastolic function were performed prior to stress testing. For systolic function, LVEF was computed using biplane Simpson measurements of end-diastolic and end-systolic volumes in the apical 4- and 2-chamber views during contrast infusion. Indexed left atrial volume, Doppler-derived pulmonary artery systolic pressure, and parameters of diastolic function assessment were recorded and graded based on American Society of Echocardiography guidelines.²⁰ MVP and WM were assessed using a 17-segment model as proposed by 2015 guidelines.²¹

DSPE Protocol

Patients were instructed to discontinue beta blockers at least 24 hours before the stress test. After measurements of baseline left ventricular systolic and diastolic function using contrast enhancement, intravenous dobutamine was infused at a starting dose of 5 µg/kg per minute, followed by increasing doses of 10, 20, 30, and 40 µg/kg per minute, up to a maximal dose of 50 µg/kg per minute, in 3- to 5-minute stages.²¹ Atropine (up to 2.0 mg) was injected in patients without symptoms or signs of myocardial ischemia not achieving 85% of the predicted maximal heart rate (220–age in years). The end points of stress tests were achievement of the target heart rate (85% of predicted maximal heart rate), maximal dobutamine/atropine doses, ST-segment elevation of 2 mm at an interval of 80 ms after the J point in non-Q-wave leads, sustained arrhythmias, severe chest pain, or intolerable adverse effects considered to be caused by dobutamine or atropine.^{22,23} Hypotension was defined as a fall of systolic blood pressure below 80 mm Hg or a reduction of >20 mm Hg from baseline. A hypertensive response was defined as a blood pressure of ≥230/120 mm Hg.²⁴

During contrast infusion, brief high mechanical index impulses were administered in each apical window, and perfusion and WM were analyzed during the myocardial replenishment period at rest and at peak stress. MVP was defined as abnormal if there was a delay in resting replenishment of myocardial contrast following a high mechanical index impulse of >4 seconds under resting conditions or >2 seconds at peak stress. The number of

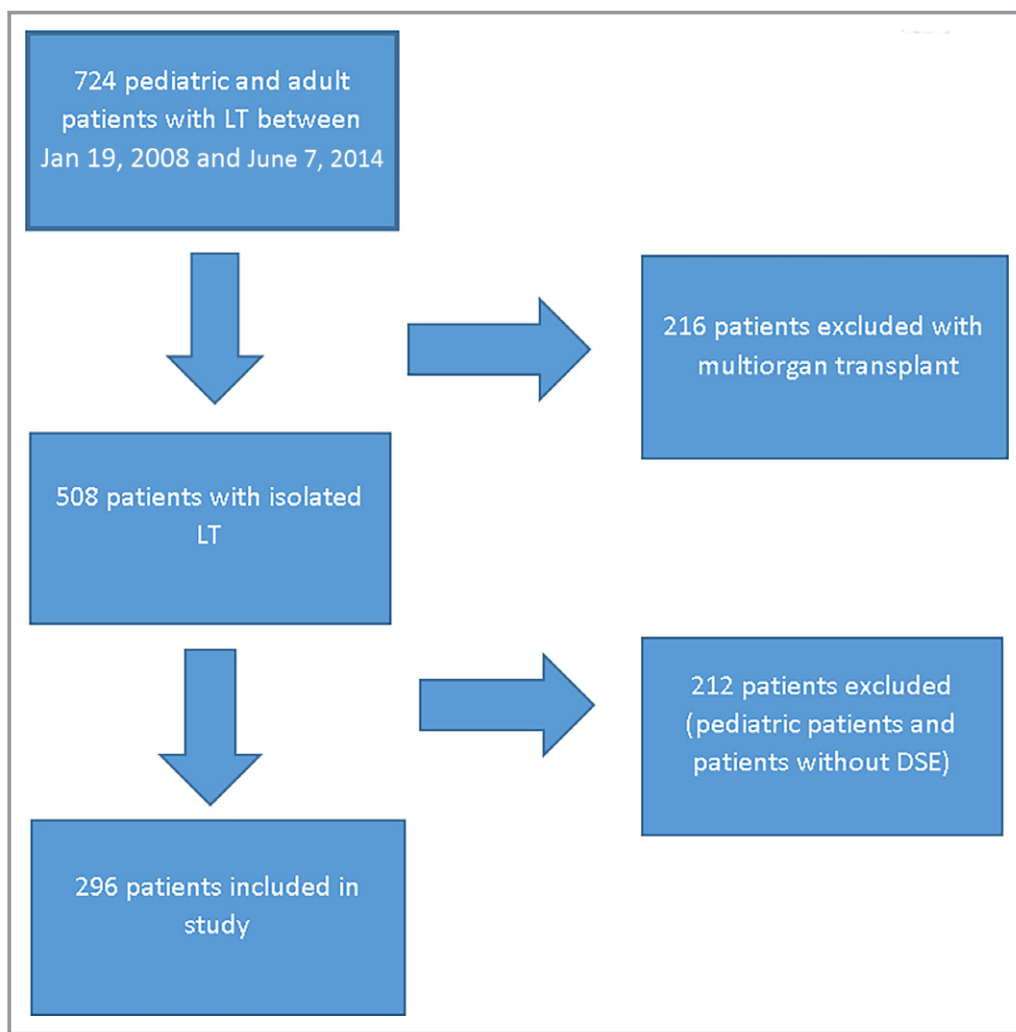


Figure 1. Flow diagram depicting how patients were selected for stress perfusion echocardiography prior to LT. DSE indicates dobutamine stress echocardiography; LT, liver transplantation.

segments exhibiting any abnormality was also quantified. WM was also segmentally graded as normal or abnormal (hypo-, a-, or dyskinetic). All WM and MVP data were interpreted by an experienced observer and then reevaluated by a second expert reviewer (F.X.) who was blinded to any clinical or other imaging data. A consensus of the 2 readers was needed to report an abnormal finding for either WM or MVP. Patients with normal MVP both at baseline and at peak stress were classified as having a normal perfusion study. Patients with normal MVP at baseline and a new segmental defect (or defects) during stress and those with baseline MVP abnormalities that persisted during stress were classified as having abnormal studies. Segments were excluded from analysis when there was attenuation from contrast or lung interference, which was defined as when the endocardial and epicardial borders of a segment could not be visualized and thus were not distinguishable from surrounding tissues.

Coronary Angiography and Revascularization

Fourteen of the 18 patients with abnormal MVP or WM were further evaluated with coronary angiography prior to LT. Revascularization with either percutaneous coronary intervention or coronary artery bypass grafting was performed based on the basis of the results of the stress test and whether $\geq 70\%$ stenosis in the proximal or midportion of a major epicardial vessel was present.

Statistical Analysis of Data

Follow-up was determined using the LT database and the electronic health records at UNMC and completed June 1, 2016. The primary outcome was considered a composite of all adverse cardiovascular events, which included cardiovascular death (death documented to occur as a result of a cardiac arrhythmia or coronary occlusive event), nonfatal myocardial infarction (defined by a serial increase in cardiac biomarkers

in the setting of a suspected acute coronary syndrome), and/or sustained ventricular arrhythmias with hemodynamic compromise. Secondary outcome was defined as a composite of all-cause death, nonfatal MI, and/or ventricular arrhythmia with hemodynamic compromise. SAS version 9.4 for PC (SAS Institute) was used for all summaries and analyses. The statistical level of significance was set at $\alpha=0.05$ for all comparisons. The years from date of transplantation to first major cardiovascular event were calculated for each participant. If a participant did not experience a major cardiovascular event, the years from date of transplantation to date of last follow-up or date of noncardiovascular death were calculated and the participant was treated as censored. Kaplan–Meier curves were generated to compare the years until the primary outcome for those with an MVP defect versus those without a defect. This was also used for abnormal versus normal WM and those with and without abnormal (grades 1–3) diastolic function. The log-rank test was used to compare these curves, and the *P* value is reported. Cox proportional hazards models were fit for both the primary and secondary outcomes. These models specifically focused on the independent predictive value of any clinical parameter, baseline assessments of LVEF and diastolic function, and any stress induced abnormality. *P* values for each term in the model were presented in addition to hazard ratios and 95% CIs. For both

the primary and secondary outcomes, univariate analyses of times to outcome were performed. Age at transplantation, LVEF, and MELD score were tested for association with each of the outcomes using Cox proportional hazards models. Clinical variables were included in this model, including diabetes mellitus, sex, and history of known CAD. The imaging and clinical variables that had *P* values <0.10 were entered into a multivariate model, and the backward selection procedure and stepwise selection were used to retain only those variables that had *P* values <0.05 in the multivariate model.

Results

Patient Characteristics

The mean age of patients at transplant was 59 ± 6 years. Overall, 197 (67%) were male and 99 (33%) were female. Of the 296 patients, 263 were white (88.8%), 14 were black (4.8%), 10 were Asian (3.3%), 6 were Hispanic (2%), and 3 were Native American (1%). In addition, 81 patients had diabetes mellitus (27%) and 121 (41%) had a history of hypertension. There were 159 patients (53%) who had a history of smoking or were current smokers.

A total of 13 patients (4.4%) had an inducible WM abnormality, and 18 patients (6%) had an inducible MVP

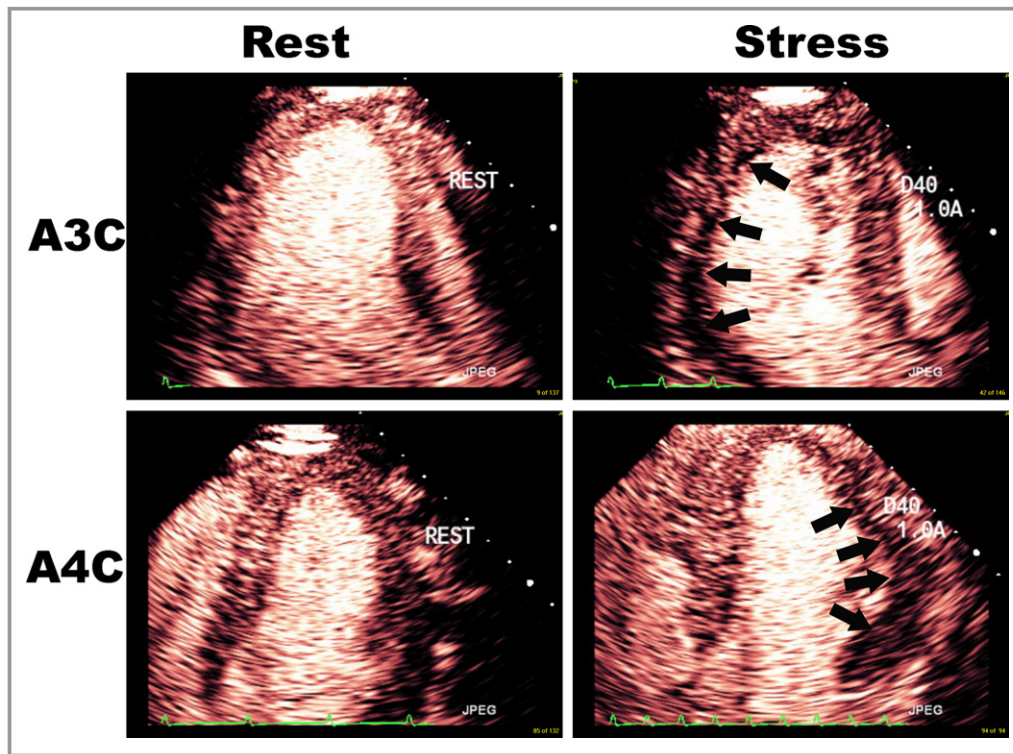


Figure 2. An example of an inducible microvascular perfusion (MVP) defect in the anterolateral and inferolateral segments (arrows) during dobutamine stress in a patient with advanced liver disease. See Video S1 for corresponding wall motion at rest/stress. A3C indicates Apical 3 Chamber view; A4C, Apical 4 Chamber view.

Table 1. Demographic and Imaging Data in Patients With Normal Versus Abnormal MVP

Variable	Normal MVP (n=276)	Abnormal MVP (n=18)	P Value
Age at transplant, y	58±6	59±6	0.6175
Sex (% male)	185 (67%)	11 (61%)	0.6058
Smoker	152 (55%)	6 (33%)	0.0731
Diabetes mellitus	74 (27%)	7 (39%)	0.2815
Hypertension	107 (39%)	12 (67%)	0.0195
Hyperlipidemia	32 (12%)	3 (17%)	0.4592
CAD	13 (5%)	6 (33%)	0.0004
NAFLD	38 (14%)	1 (6%)	0.4842
MELD score	20±9	24±14	0.2603
LVEF, %	64±6	60±11	0.1446
Pulmonary artery systolic pressure, mm Hg	29±8	32±6	0.1086
E, cm/s	81±19	77±18	0.3240
e', cm/s	10±3	11±4	0.2843
Normal diastolic function	173 (63%)	11 (61%)	0.8630

CAD indicates coronary artery disease; LVEF, left ventricular ejection fraction; MELD, Model for End-Stage Liver Disease; MVP, microvascular perfusion; NAFLD, nonalcoholic fatty liver disease.

defect (Figure 2, Video S1). There were no resting WM or MVP defects (no fixed defects). All patients with inducible WM abnormality had inducible MVP abnormality, whereas 5 patients had inducible MVP defects but no inducible WM abnormality. Table 1 describes the differences in clinical and baseline imaging variables in those with normal versus abnormal MVP responses. There was no significant difference between these groups in terms of age, sex, smoking history,

Table 2. Causes of End-Stage Liver Disease

Etiology	n (%)
Hepatitis C	74 (25)
Nonalcoholic steatohepatitis	39 (13)
Malignancy	36 (12)
Alcohol	35 (12)
Alcohol and hepatitis C	23 (8)
Primary biliary cirrhosis	14 (5)
Primary sclerosing cholangitis	14 (5)
Autoimmune hepatitis	13 (4)
Cryptogenic	12 (4)
α1-Antitrypsin deficiency	11 (4)
Hepatitis B and C	5 (2)
Hepatitis B	3 (1)
Other causes	17 (6)

diabetes mellitus, hyperlipidemia, or prevalence of nonalcoholic fatty liver disease. Patients with MVP defects had significantly higher prevalence of known prior CAD ($P=0.004$) and hypertension ($P=0.02$).

Table 2 describes the etiology of liver cirrhosis in the 296 patients included in the study. The most common causes of end-stage liver disease were hepatitis C, nonalcoholic fatty liver disease, and alcoholic liver disease.

Outcomes

Fourteen of the 18 patients with abnormal DSPE studies underwent coronary angiography prior to LT. Seven (50%) were found to have significant obstructive epicardial lesions and underwent revascularization with either percutaneous coronary intervention (3 patients) or coronary artery bypass grafting (4 patients) prior to transplantation. The median follow-up time was 4.1 years for the primary outcome and 4.8 years for the secondary outcome. Over the median follow-up period, 69 patients died (23%). The causes of noncardiovascular death in 65 patients were as follows: 14 with graft failure, 12 with postsurgical and bleeding complications, 9 with sepsis, 8 with multiorgan dysfunction, 8 with malignancy, 1 with renal failure, 1 with insulin overdose, and 12 with exact cause unknown.

Abnormal MVP was a significant univariate predictor of the primary outcomes, as was the presence of an inducible WM abnormality (Figure 3A and 3B). Patients with MVP defects had significantly higher cumulative incidence of the primary outcome compared with patients with normal stress MVP (16% versus 0.7%, $P=0.0006$), whereas those with abnormal WM also had significantly higher incidence (15% versus 1%, $P=0.008$). Diastolic dysfunction was not predictive of the primary outcome, even when comparing patients with grade 2–3 diastolic dysfunction with those who had normal function or grade 1 dysfunction. There was a tendency for abnormal MVP ($P=0.19$) (Figure 4) and abnormal diastolic function ($P=0.13$) to predict the secondary composite outcome, but no specific rest or stress variable predicted overall mortality. On multivariate analysis after adjusting for confounding clinical and imaging variables (age, diabetes mellitus, MELD score, history of CAD, LVEF, diastolic dysfunction, WM abnormality), only abnormal MVP was an independent predictor of the primary outcome ($P<0.001$). Patients with an MVP defect at peak stress had a 7.5-fold increased risk of experiencing primary outcome following transplantation in a multivariate model (95% CI 1.9–30.7). MVP was an independent predictor of the primary outcome when using both stepwise selection and backward variable selection methods.

Table 3 describes the demographic characteristics, stress test findings, and outcomes of the 18 patients with abnormal MVP. Two of the 5 patients (40%) with abnormal MVP but

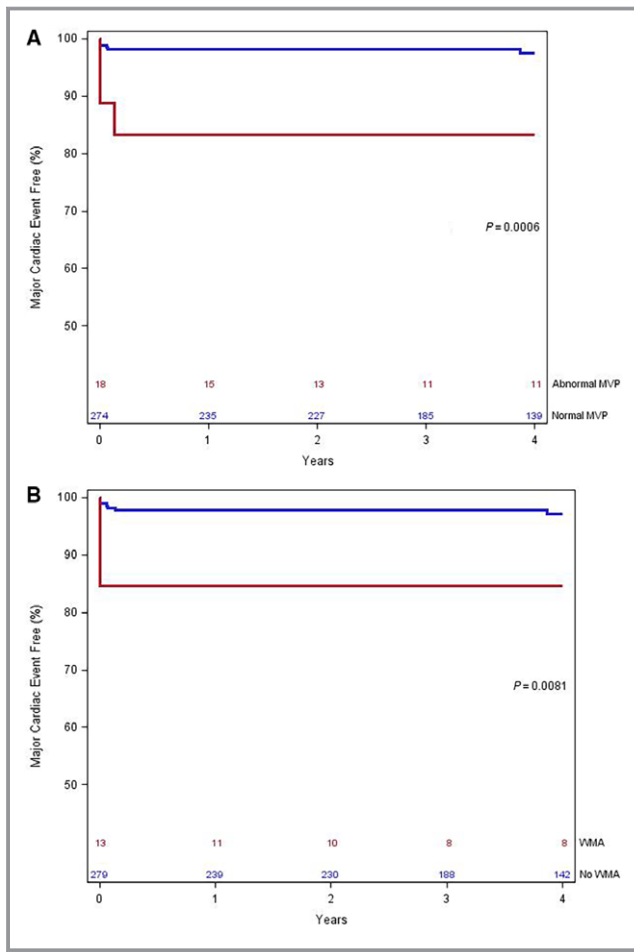


Figure 3. Kaplan–Meier curves depicting primary-outcome event-free survival for patients with abnormal vs normal stress microvascular perfusion (A) and abnormal vs normal wall motion (B). MVP indicates microvascular perfusion; WMA, wall motion abnormality.

normal WM had cardiovascular deaths after LT. Of the 4 patients with abnormal MVP who did not have coronary angiography, 1 (25%) had a primary event; this was not different than the primary event rate in those who did go on to angiography.

Discussion

Noninvasive stress tests in candidates for LT have typically been performed using pharmacological stressors because patients with advanced liver disease are usually debilitated and also may have chronotropic incompetence.²⁵ In this setting, either vasodilator radioisotope imaging (analyzing myocardial perfusion only) or dobutamine stress echocardiography (analyzing WM only) have been used. Contrast-enhanced echocardiography is now frequently used during stress echocardiography to improve endocardial border resolution for LVEF determination and WM analysis.²⁶ MVP

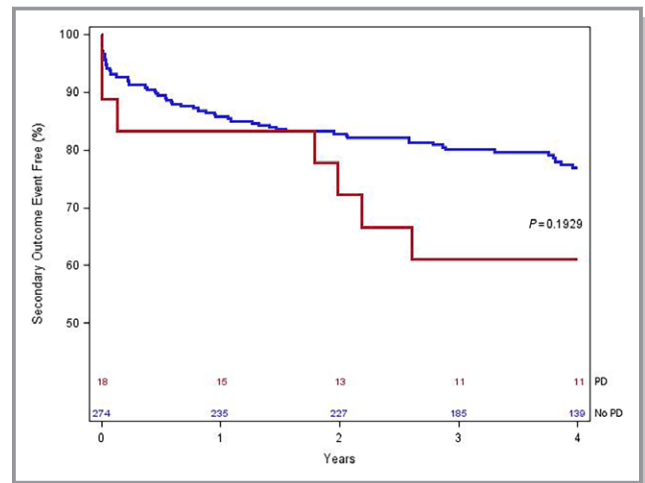


Figure 4. Kaplan–Meier curves depicting secondary-outcome event-free survival (including all-cause death) for patients with abnormal vs normal stress microvascular disease. PD indicates perfusion defects.

imaging is now possible with the same contrast infusion dose required to improve endocardial border delineation. Although an “off-label” use, this technique has been shown to have several advantages over WM analysis alone. MVP imaging with real-time perfusion echocardiography allows concurrent analysis of stress WM and myocardial blood flow,¹⁷ unlike any other noninvasive imaging modality available. Studies have demonstrated improved detection of epicardial CAD when real-time perfusion echocardiography is combined with WM analysis.²⁷ In patients with intermediate pretest probability of CAD, MVP analysis during stress real-time perfusion echocardiography provides independent and incremental prognostic data compared with WM analysis alone.^{16,27}

Microvascular disease has been shown to be associated with significantly increased risk of adverse cardiac events, which include sudden death and myocardial infarction.^{28,29} The major finding of the current study is that abnormal stress-induced MVP was a significant independent predictor of cardiovascular outcomes. We found that MVP imaging was associated with occult epicardial disease that led to revascularization in 7 (38%) of 18 patients with abnormal DSPE; however, 7 of 14 patients (50%) with MVP defects during stress did not have significant obstructive epicardial CAD. Despite revascularization in the subset of patients with abnormal MVP, the entire group of patients with abnormal stress MVP still had worse outcomes compared with those with normal MVP responses. This would indicate that detection of a stress-induced MVP defect prior to LT evaluation warrants more than just coronary angiography and epicardial revascularization if a significant stenosis is detected. Although the number of abnormal MVP studies was small relative to the entire study population, the presence of MVP defects during stress (regardless of epicardial disease

Table 3. Characteristics and Outcomes in Patients With Perfusion Defects and Wall Motion Abnormality

Demographics	Risk Factors	LVEF	MVP, No. Positive Segments	WM, No. Positive Segments	Angiography/Revascularization	Outcome
49 male	HTN, smoking	60%	3	3	No significant epicardial CAD	No adverse outcome
55 male	HTN, smoking	55%	6	6	2 vessel disease, underwent CABG	No adverse outcome
66 female	HTN, Hyperlipidemia	73%	3	None	No angiography performed	No adverse outcome
50 female	HTN, DM	60%	5	5	No significant epicardial CAD	No adverse outcome
52 male	Hyperlipidemia	60%	2	2	No significant epicardial CAD	No adverse outcome
62 male	HTN, DM, smoker, CAD	70%	4	4	2 vessel disease, PCI to LAD and RCA	Non cardiovascular death
56 female	HTN, DM, CAD	60%	3	None	Obstructive LAD disease, LIMA to LAD	Non cardiovascular death
62 female	None	61%	2	2	No significant epicardial CAD	No adverse outcome
52 male	None	65%	2	None	No significant epicardial CAD	No adverse outcome
57 male	HTN, smoker, CAD	60%	2	2	2 vessel disease, CABG with LIMA to LAD and SVG to LCX	Non cardiovascular death
68 female	HTN	60%	3	3	No significant epicardial CAD	Nonfatal MI
58 male	HTN, DM, smoker, CAD	70%	3	3	LCX disease, PCI of mid- LCX	Cardiovascular death I
69 female	HTN, CAD	67%	4	4	Multivessel disease, CABG (of the 18 patients with abnormal DSPE)	No adverse outcome
54 male	DM	50%	2	None	No angiography performed	Cardiovascular death
62 male	DM, smoker	54%	2	None	No angiography performed	No adverse outcome
	HTN, hyperlipidemia	60%	2	2	LAD and diagonal disease, PCI of LAD and Diagonal	No adverse outcome
61 male	HTN, DM	72%	3	3	No angiography performed	No adverse outcome
70 female	HTN, DM	65%	2	2	No significant epicardial CAD	No adverse outcome

Patients with abnormal MVP during dobutamine stress, with subsequent angiographic results and clinical outcome. CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; DM, diabetes mellitus; DSPE, dobutamine stress perfusion echocardiography; HTN, hypertension; LAD, left anterior descending artery; LCX, left circumflex artery; LIMA, left internal mammary artery grafting; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MVP, microvascular perfusion; PCI, percutaneous coronary intervention; RCA, right coronary artery; SVG, saphenous vein graft; WM, wall motion.

and subsequent revascularization) was the only independent predictor of cardiovascular events. Although the mechanisms for inducible MVP defects in the absence of significant obstructive epicardial disease are unknown, the risk factors for inducible MVP may be similar to overt epicardial CAD.³⁰ Consequently, control of blood pressure and serum lipids in patients exhibiting MVP defects during demand stress may be critical in the post-LT setting, where recovery of liver function combined with antirejection therapies may increase the risk of hypertension and dyslipidemia.

Study Limitations

This study was a retrospective single-center study and included only patients who underwent LT. This selection bias could have underestimated the prevalence of CAD, and there may have been patients who were declined LT because of known significant cardiac disease or structural cardiac dysfunction prior to LT evaluation. Moreover, we demonstrated only a trend for inducible MVP defects or diastolic dysfunction to predict all-cause deaths. This may be related to

the fact that a good percentage of post-LT all-cause deaths were caused by graft rejection and postoperative bleeding, which may not be predicted by MVP responses to stress. We evaluated for outcomes after LT only in patients who had undergone DSPE. Many patients wait for a long period of time before they get LT, and there could have been cardiovascular events that occurred during that period, especially in those with bleeding events or prolonged hypotension.

Conclusions

The assessment of MVP with DSPE appears to be a useful noninvasive technique to risk-stratify patients with end-stage liver disease undergoing LT in the current era. Abnormal MVP during demand stress identified patients with significant epicardial CAD as well as coronary microvascular dysfunction without epicardial CAD. Despite revascularizing all patients with abnormal MVP and significant epicardial disease, there was a >7-fold increased risk of cardiovascular death and nonfatal myocardial infarction in patients with abnormal MVP.

The detection of inducible MVP defects adds incremental predictive value over WM analysis, resting left ventricular systolic and diastolic function, and clinical variables in predicting cardiovascular outcome in the current patient population undergoing LT.

Acknowledgments

The authors want to thank Carol Gould for her dedicated work in preparing the manuscript and the Theodore Hubbard Foundation for funding the costs associated with manuscript preparation.

Sources of Funding

This study was supported in part by the Theodore F. Hubbard Foundation.

Disclosures

None.

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