Utility of Dobutamine Stress Echocardiography in Cardiac Risk Stratification of Patients Undergoing Orthotopic Liver Transplantation

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Cardiovascular diseases are a major cause of morbidity and mortality in patients after orthotopic liver transplantation (OLT). This review includes major original articles published in the English-language literature of patients who underwent dobutamine stress echocardiography (DSE) before OLT for cardiac risk stratification. Of a total of 10 original articles (total 1699 patients undergoing DSE), 6 studies used DSE to predict major adverse cardiac events (MACE) in patients undergoing OLT and 4 reported the role of DSE in coronary artery disease (CAD) prediction in patients with end-stage liver disease. The composite incidence of MACE was 11.4%. In predicting postoperative MACE, DSE had a composite sensitivity of 0.12 (95% CI, 0.07-0.19), a specificity of 0.96 (95% CI, 0.94-0.97), a positive predictive value (PPV) of 0.26 (95% CI, 0.16-0.38), and a negative predictive value (NPV) of 0.89 (95% CI, 0.88-0.91). The presence of known CAD in a patient was shown to increase the risk of cardiac events after OLT significantly in three of six studies. The average prevalence of CAD was 14.4%. In predicting CAD, DSE had a composite sensitivity of 0.47 (95% CI, 0.32-0.62), specificity of 0.74 (95% CI, 0.68-0.79), PPV of 0.23 (95% CI, 0.15-0.33), and NPV of 0.89 (95% CI, 0.84-0.93). This review emphasizes the need for standardizing cardiac risk stratification protocol to screen and prevent cardiac morbidity after OLT, standardizing MACE definition to allow more uniform reporting, and the need for safer and efficacious alternatives to DSE in the evaluation of OLT candidates.

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KEY WORDS

Dobutamine stress echocardiography • Cardiovascular event • Liver transplantation • Coronary artery disease

Liver transplantation is the established treatment modality for patients with end-stage liver disease (ESLD). Approximately 7000 liver transplantations are performed each year in United States.[1] According to the United Network for Organ Sharing registry, the survival rate for patients after liver transplantation at 1, 5, and 10 years is 85%, 70%, and 50%, respectively.[2] Among patients undergoing orthotopic liver transplantation (OLT), cardiovascular disease is the leading cause of 30-day mortality.[3] In addition, it continues to be the second most important cause of morbidity and mortality after malignancy in a 10-year median follow-up after OLT.[4]

Because of the extensive risk of hemodynamic instability with liver transplantation,[5] patients considered for OLT undergo comprehensive preoperative evaluation, including cardiac risk stratification. The American Association for the Study of Liver Disease recommends an echocardiogram for all liver transplantation candidates.[6] They further state, "cardiac evaluation needs to include assessment of cardiac risk factors with stress echocardiography as an initial screening test with cardiac catheterization as clinically indicated." Dobutamine stress echocardiography (DSE) is frequently used as the initial screening test. In this article, we summarize all original studies that have used DSE as a modality to predict major adverse cardiovascular events (MACE) or for the prediction of coronary artery disease (CAD) in patients undergoing liver transplantation.

Methods

An extensive English language literature search was done using PubMed, Medline, and Google Scholar to identify articles using keywords *liver transplant*, *dobutamine stress echocardiography*, *cardiovascular event*, and *CAD*. Human-only articles were selected. A study by Baibhav and colleagues[7] was excluded from the initial search results due to the use of dobutamine stress perfusion echocardiography and assessment of microvascular perfusion in contrast to the conventional DSE. The references of pertinent studies were manually searched to identify additional relevant studies. The indications of DSE, incidence of MACE and CAD, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of DSE in predicting MACE and CAD, and complications of DSE for each study were reviewed.

Results

All 10 original studies considered appropriate to be included in our review article are from the United States; 9 are retrospective and 1 is prospective. These studies were divided into two sets. The first set includes studies using DSE as a tool to predict MACE, summarized in Table 1.[8-13] The second set includes studies using DSE in predicting CAD, summarized in Table 2.[5,14-16] Across the six studies included in the first set, 1820 liver transplantation candidates were evaluated.[8-13] Among them, 1185 patients underwent DSE. The population had a mean age of 54 years with a 64% predominance in men.[8-13] Patients were followed for MACE for different time periods in different studies varying from 30 days to 4.4 years after OLT.[8-13] Across the four studies included in the set, 2514 patients underwent DSE and 327 had left heart catheterization (LHC).[5,14-16] LHC was considered the gold standard to diagnose CAD in these four studies. The mean age of patients was 54.5 years, with a 62% predominance in men.[5,14-16]

Discussion

Indications for DSE

The indications to undergo DSE for transplantation evaluation varied among the studies. Two studies (by Safadi and associates[8] and Nicolau-Raducu[9] and associates), utilized DSE before liver transplantation as a "routine practice," with no specific indications. Umphrey and coworkers[10] performed DSE on patients with one or more of the following, including age >45 years, history of diabetes, history of peripheral vascular disease (PVD), or presence of >2 Framingham Risk Score cardiac risk factors. Findlay and associates[11] performed DSE on patients with history consistent with CAD, symptoms concerning for CAD, diabetes, hypertension, arrhythmia, history of significant arrhythmia, family history of CAD, age >50 years, or obesity. Williams and associates[12] reported DSE results in patients with one or more of the following: cardiac risk factors (hypertension, diabetes, hypercholesterolemia, ≥20 pack-year of tobacco use), atypical chest pain, nonspecific cardiopulmonary symptoms, or age ≥60 years. Lastly, in the study by Snipelisky and colleagues,[13] whether to undergo DSE or not was at the discretion of the physician.

TABLE 1

Descriptive Summary of Individual Studies

Study	Type of Study	Patients Evaluated (N)	Patients Undergoing DSE (n)	Mean Age (y)	Sex	MACE	Follow-up Period	Incidence of MACE	Cardiac Risk Factors	Outcome	
Safadi A et al[8]	Retro-spective	403	356	51.5 ± 9.4	Men 270 (67%), women 133 (33%)	Nonfatal MI & death	30 d	Total patients with MACE: 48 (12%); MI events: 25 (7%); death events: 38 (9%)	h/o CAD predicted greater risk (P =.014)	DSE (+) MACE (+): 7 DSE (+) MACE (−): 16 DSE (−) MACE (−): 41 DSE (−) MACE (−): 292	Sensitivity 0.14; specificity 0.95; PPV 0.27; NPV 0.89
Nicolau-Raducu R et al[9]	Retro-spective	389	278 Target HR achieved in 195 patients (N = 195)	55 (50-60)	Men 254 (65%), women 135 (35%)	ACS (nonfatal MI, fatal MI, unstable angina), new onset of HF, arrhythmia, resuscitated cardiac arrest, CVA, and PVD	3.4 y (range 2.3-4.4 y)	1 y: 23 (11.8%) cardiac events (6 nonfatal MI, 7 nonfatal acute HF, 3 arrhythmias, 2 atrial fibrillation, 5 cardiac death); 1 mo: 38 (9.8%); 1 y: 59/389 (15.2%); 1-y mortality: 32 (8.2%); 1 y ACS: 21 (5.4%); late CV morbidity: 14 (3.9%); 3.4-y mortality; 66 (17%),	Age (P <.001) and h/o CAD (P <.001) significant for post-transplant ACS	DSE (+) MACE (+): 2 DSE (+) MACE (−): 4 DSE (−) MACE (+): 21 DSE (−) MACE (−): 168	Sensitivity 0.09; specificity 0.98; PPV 0.33; NPV 0.89
Umphrey LG et al[10]	Retro-spective	284	157	54.5 ± 7.5	Men 112 (71%), women 45 (29%)	VT, asystole, MI and new heart failure	4 mo	16 (10%), 9 of these at the time of surgery	None had significant difference	DSE (+) MACE (+): 0 DSE (+) MACE (−): 0 DSE (−) MACE (+):16 DSE (−) MACE (−): 141	Sensitivity 0; specificity 1; PPV; NPV 0.89

Findlay JY et al[11]	Retrospective	117	73	52 ± 10	Men 61 (52.1%), women 56 (47.9%)	Troponin elevation	NA	10 (13.6%)	NA	DSE (+) MACE (+): 2 DSE (+) MACE (−): 6 DSE (−) MACE (+): 8 DSE (−) MACE (−): 57	Sensitivity 0.20; specificity 0.90; PPV 0.25; NPV 0.88
						Significant hemodynamic event[a]		18 (24.6%)		DSE (+) MACE (+): 3 DSE (+) MACE (−): 5 DSE (−) MACE (+): 15 DSE (−) MACE (−): 50	Sensitivity 0.16; specificity 0.90; PPV 0.37; NPV 0.77
Williams K et al[12]	Retrospective	121 (61 underwent liver transplant)	61	53 (34-73)	Men 77 (63.6%), women 44 (36.4%)	Atrial fibrillation, cardiac arrest, AVNRT, ventricular fibrillation		8 (13%)	NA	DSE (+) MACE (+): 0 DSE (+) MACE (−): 2 DSE (−) MACE (+): 8 DSE (−) MACE (−): 51	Sensitivity 0; specificity 0.96; PPV 0; NPV 0.86
Snipelisky D et al[13]	Retrospective	506	343	58.2 ± 7.3	Men 226 (65.9%), women 117 (34.1%)	Not defined	6 mo	Perioperative: 20 (5.8%); postoperative: 3 (0.9%); cardiac death: 4 (1.2%)	h/o previous CAD higher in DSE positive individuals ($P < .01$)	DSE (+) MACE (+): 3 DSE (+) MACE (−): 16 DSE (−) MACE (+): 17 DSE (−) MACE (−): 307	Sensitivity 0.15; specificity 0.95; PPV 0.16; NPV 0.95

[a]Significant hemodynamic event defined as hypotension (systolic blood pressure < 80 mm Hg for > 10 sequential minutes, requirement of pressor, significant new arrhythmia including cardiac arrest.

ACS, acute coronary syndrome; AVNRT, atrioventricular nodal reentrant tachycardia; CAD, coronary artery disease; CVA, cerebrovascular accident; DSE, dobutamine stress echocardiography; MACE, major adverse cardiac event; MI, myocardial infarction; NA, not available; NPV, negative predictive value; PPV, positive predictive value; PVD, peripheral vascular disease; VT, ventricular tachycardia.

This reflects a wide heterogeneity in the indications for DSE in patients undergoing OLT. The American Heart Association recommends that invasive stress testing be considered in liver transplantation candidates with no active cardiac conditions on the basis of the presence of multiple CAD risk factors regardless of functional status. They further state, "relevant risk factors among transplantation candidates include diabetes, prior cardiovascular disease, left ventricular hypertrophy, age >60 years, smoking, hypertension, and dyslipidemia." The specific number of risk factors that should be used to prompt testing remains to be determined, but the committee considers three or more to be a reasonable indication (Class IIb; Level of Evidence C).[17]

The American Heart Association recommends invasive stress testing to be considered in liver transplantation candidates with no active cardiac conditions on the basis of the presence of multiple CAD risk factors regardless of functional status.

The heterogeneity in the selection criteria suggests the need for better understanding of association between cardiac risk factors and MACE in OLT candidates. A more uniform evidence-based approach may help in standardizing the cardiac risk stratification protocol for patients before OLT.

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MACE Definition and Incidence

Recently Konerman and coworkers[18] conducted a systematic review involving 57,493 patients stating that true incidence of cardiovascular outcomes after liver transplantation remains unknown due to the lack of consensus regarding the outcome definition and poor data quality. MACE in the six included studies in this review were acute coronary syndromes, nonfatal myocardial infarction, fatal myocardial infarction, troponin elevation, unstable angina, new-onset heart failure, cardiac arrest, cerebrovascular accident, PVD, and arrhythmias such as ventricular tachycardia, asystole, atrial fibrillation, atrioventricular nodal reentrant tachycardia, and ventricular fibrillation.[8-13]

The majority of MACE were myocardial infarction (47/162, 29%) and death (47/162, 29%). Other observed MACE were arrhythmia (16/162, 9.9%), significant hemodynamic events (18/162, 11.1%), heart failure (7/132, 4.3%), and atrial fibrillation (5/162, 3%). Significant hemodynamic event was defined as hypotension (systolic blood pressure <80 mm Hg for >10 sequential min, requirement of pressor, significant new arrhythmia including cardiac arrest).[11] One study did not report the different types of events and hence have been classified as unknown (20/162, 12.3%) in the above analysis.[13] The total incidence of MACE in each study varied from 5.8% to 24.6%.[12,13] A pictorial depiction of incidence of each different type of MACE is shown in Figure 1 and details are summarized in Table 1. The patients were followed for different time periods across different studies. This highlights the need for a standard definition for MACE that can be reported uniformly in future studies.

Cardiac risk stratification continues to be a dilemma for many liver transplantation centers.

MACE Prediction

Cardiac risk stratification continues to be a dilemma for many liver transplantation centers. Most studies do not report the predictive value of DSE for each individual

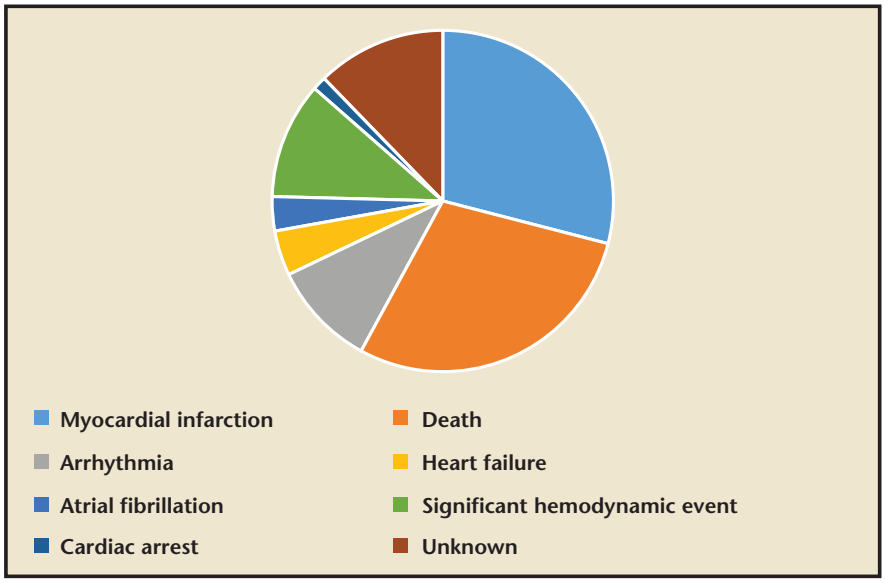

Figure 1. Types of major adverse cardiovascular events across six studies.

MACE event, and only mention a cumulative sensitivity, specificity, NPV, and PPV for all MACE.[8-10,12,13] In the study by Findlay and associates,[11] DSE was reported to have a sensitivity of 0.2, a specificity of 0.9, a PPV of 0.25, and an NPV of 0.88 in predicting troponin elevation after OLT, but had a marginally lower sensitivity and NPV to predict a significant hemodynamic event (sensitivity 0.16, specificity 0.9, PPV 0.37, NPV 0.77). In predicting MACE, all studies showed that DSE had low sensitivity, varying from 0 to 0.20, low PPV (0-0.37), great specificity (0.90-1.0), and reasonable NPV (0.77-0.95).[8-13] The composite incidence of MACE was 11.4%. In predicting postoperative MACE, DSE had a composite sensitivity of 0.12 (95% CI, 0.07-0.19), specificity of 0.96 (95% CI, 0.94-0.97), PPV of 0.26 (95% CI, 0.16-0.38), and NPV of 0.89 (95% CI, 0.88-0.91).

DSE had low composite sensitivity (0.12) in predicting MACE, proving its inability to correctly identify patients who can develop MACE after OLT. However, it had a composite specificity of 0.96, qualifying it as a test to correctly identify patients without MACE after OLT. Figure 2 illustrates an example of a high-risk DSE result.

Multiple other modalities have been tested to screen for CAD before OLT. These include computed tomographic angiography and coronary calcium scoring, single-photon emission computed tomography (SPECT), myocardial perfusion imaging (MPI), and cardiopulmonary exercise testing. Each has its own limitations. Computed tomographic angiography with coronary calcium scoring and SPECT MPI are both hindered by high rates of false-positive results.[19,20] It is postulated that, due to the systemic vasodilation seen in chronic liver disease, the sensitivity and specificity of MPI is reduced in the liver transplantation candidate population. Newer imaging modalities should be studied in more depth to find their roles in preoperative risk stratification.

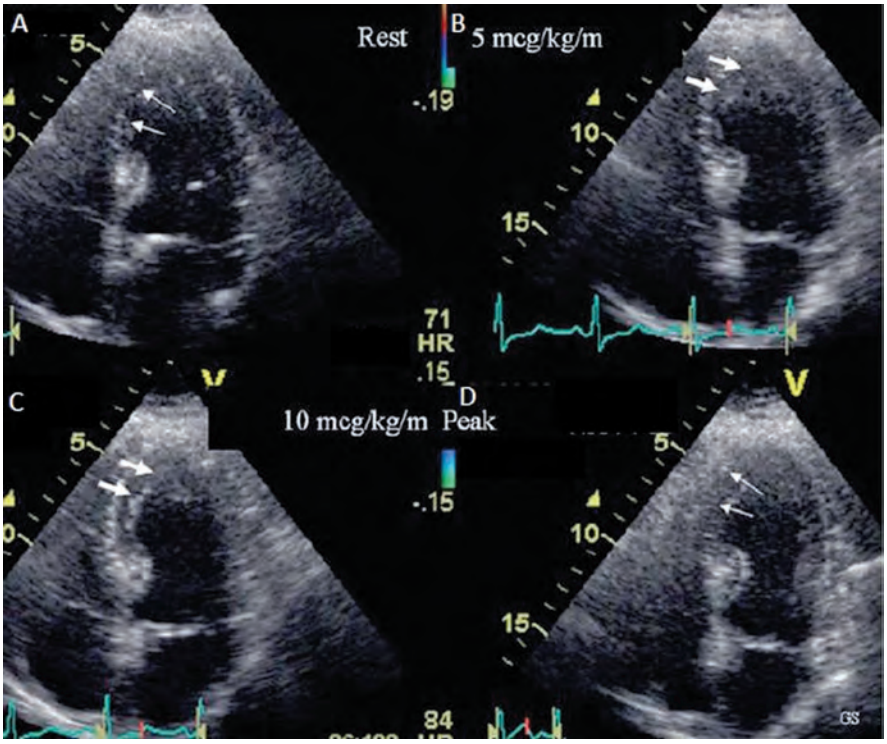

Figure 2. Dobutamine stress echocardiogram of a patient with biphasic response during dobutamine infusion and high-risk ischemia in the left anterior descending coronary artery territory. These serial four-chamber echocardiograms show hypokinesis of the mid to distal septum and apex at rest, which improve at low dose (5 and 10 µg/kg/min) and become akinetic during peak dose.

prevalence of CAD across these four studies was 14.4%. Though all studies used LHC findings to define CAD, the study by Plotkin and colleagues,[14] the only prospective study, made an assumption that patients with normal DSE and normal cardiac outcome after OLT had normal coronary arteries or at worst clinically insignificant CAD. These studies have been summarized in Table 2. According to the Centers for Disease Control and Prevention, the age-adjusted coronary heart disease prevalence in the United States was approximately 6% in 2010.[21] Carey and associates[22] reported an overall prevalence of severe CAD in patients with ESLD of 16.2% (N = 37), similar to the average in our review. They also showed that diabetes was the most predictive risk factor for CAD.[22]

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Prevalence of CAD in ESLD Patients

Among the four studies investigating the role of DSE in predicting CAD, we found that the prevalence of CAD in patients with ESLD varied from 3% to 27%. Patel and colleagues[16] differentiated the prevalence of CAD on the basis of etiology of ESLD, mentioning alcohol-related ESLD to have much lower CAD prevalence than non–alcohol-related ESLD (3% vs 27%). The other studies had CAD prevalence of 5%, 22%, and 27%, respectively.[5,14,15] The average

TABLE 2

Study Descriptions and Outcomes

Study	Type of Study	Patients Evaluated (N)	Patients Undergoing DSE (n)	Mean Age (y)	Sex (%)	Patients With LHC (n)	CAD Incidence (%)	Study Outcomes	
Plotkin JS et al[14]	Prospective	220	80 (N = 40, follow-up data availability, used for calculations)	51.2 (35-70)	Men 23 (57.5), women 17 (42.5)	21[a]	2/40 (5)[a]	DSE (+) CAD (+): 2 DSE (+) CAD (−): 4 DSE (−) CAD (+): 0 DSE (−) CAD (−): 34	Sensitivity 1; specificity 0.9; PPV 0.33; NPV 1
Harinstein ME et al[15]	Retrospective	64 (21 underwent OLT)	64 (21 underwent OLT)	61±8	Men 45 (70.3), women 19 (29.7)	64	16 (27)	DSE (+) CAD (+): 2 DSE (+) CAD (−): 7 DSE (−) CAD (+): 14 DSE (−) CAD (−): 41	Sensitivity 0.13; specificity 0.85; PPV 0.22; NPV 0.75
Donovan CL et al[5]	Retrospective	190	165 (71 underwent OLT)	50 (26-70)	Men 98 (52), women 92 (48)	18	4 (22.2)	DSE (+) CAD (+): 3 DSE (+) CAD (−): 6 DSE (−) CAD (+): 1 DSE (−) CAD (−): 8	Sensitivity 0.75; specificity 0.57; PPV 0.33; NPV 0.89
Patel S et al[16]	Retrospective	420	205	56±8	Men 279 (66.4), women 141 (33.6)	205	Alcohol-related ESLD: 2 (3)	DSE (+) CAD (+): 1 DSE (+) CAD (−): 10 DSE (−) CAD (+): 2 DSE (−) CAD (−): 52	Sensitivity 0.33; specificity 0.84; PPV 0.09; NPV 0.96
							Non–alcohol-related ESLD: 38 (27)	DSE (+) CAD (+): 14 DSE (+) CAD (−): 46 DSE (−) CAD (+): 8 DSE (−) CAD (−): 72	Sensitivity 0.64; specificity 0.61; PPV 0.23; NPV 0.90

[a]Assumption made that patients with a normal DSE result and normal cardiac outcome after OLT had normal coronary arteries or at worst clinically insignificant CAD; therefore, though the number of patients undergoing LHC was 21, the total population for calculation was taken as 40 by the study.

CAD, coronary artery disease; DSE, dobutamine stress echocardiography; LHC, left heart catheterization; OLT, orthotopic liver transplantation; PPV; positive predictive value; NPV, negative predictive value.

Patel and colleagues[16] showed that presence of ≥1 CAD risk factor was associated with significant CAD ($P < .05$). Realizing such a high prevalence of CAD in patients with ESLD, it's important to find tools to better predict CAD to prevent adverse cardiovascular outcomes.

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CAD Prediction

There is a paucity of data on accuracy of DSE in screening ESLD patients for significant CAD. Across the four studies in our review, DSE had a composite sensitivity of 0.47 (95% CI, 0.32-0.62), specificity of 0.74 (95% CI, 0.68-0.79), PPV of 0.23 (95% CI, 0.15-0.33), and NPV of 0.89 (95% CI, 0.84-0.93) in predicting CAD.[5,14-16] The sensitivity varied the most, ranging from 0.13 to 1.[14,15] A high NPV helps predict the absence of CAD in patients with a negative DSE result accurately. However, a positive DSE result poorly predicts the presence of CAD (sensitivity 0.47). It will be interesting to learn the prospective follow-up of these patients with CAD to find the incidence of adverse cardiac event after liver transplantation. We, henceforth, reiterate the need for larger, prospective studies to find a good screening tool for predicting CAD in patients undergoing OLT.

Etiology of MACE

An adverse cardiac event could be due to the inherent cardiac risk factors, the intraoperative course such as blood loss or surgical stress, the adverse effect of immunosuppressive agents, or a combination of these factors. Pisano and coworkers[23] summarized the metabolic side effects of immunosuppressive medications such as hypertension, hyperlipidemia, diabetes, obesity, and insulin resistance, which can be contributory to increased metabolic syndrome and hence cardiovascular disease in patients after transplantation. Nicolau-Raducu and colleagues[9] stated that age ($P < .001$) and history of CAD ($P < .001$) were both significant predictors for post-transplant acute coronary syndromes. The study by Safadi and associates,[8] using a multivariate model, demonstrated that a history of CAD ($P = .014$), prior stroke ($P = .025$), and postoperative sepsis ($P < .001$) predicted a greater risk for MACE. Although these two studies showed the presence of previous CAD to be a significant risk factor, the study by Umphrey and associates[10] showed no significant difference among the CAD risk factors in patients with and without cardiac events after OLT. Interestingly, the study by Safadi and associates[8] showed the use of perioperative β-blockers to be protective for cardiac outcomes ($P = .004$). A large study is needed to assess the protective and the significant contributing factors for worse cardiac outcomes in these patients undergoing liver transplantation to design a protocol for better cardiac risk stratification.

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Complications of DSE

Complications, such as arrhythmia and hypotension, occur after administration of dobutamine and atropine. Reports in smaller populations show a 10% to 14% occurrence of hypotension during DSE.[24-26] One of the six studies reported the complication rate of 17% (21/121), including hypotension (7.4%), chest pain (4.9%), nausea and vomiting (3.3%), hypertension (0.8%), and ventricular bigeminy (0.8%).[12] These complications were managed conservatively. The high incidence of hypotension may be attributed to the baseline systemic vasodilation in patients with chronic liver disease. The high complication rate stresses the need for a safer and more efficacious alternative to DSE.

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Summary and Future Directions

Although the advancing surgical technique and newer antirejection drugs are improving the survival of patients after OLT, cardiovascular morbidity and mortality remain an obstacle. Our review included 10 original articles with a total of 1699 patients who underwent DSE before OLT for cardiac risk stratification. Six studies used DSE to predict MACE in patients undergoing OLT and four reported the role of DSE in CAD prediction in patients with ESLD. The composite incidence of MACE was 11.4%. In predicting postoperative MACE, DSE had a rather low composite sensitivity of 0.12 (95% CI, 0.07-0.19) but a high

specificity of 0.96 (95% CI, 0.94-0.97). The PPV was low at 0.26 (95% CI, 0.16-0.38) and the NPV was high at 0.89 (95% CI, 0.88-0.91). A high NPV predicts the absence of significant MACE in the setting of a negative DSE. The presence of known CAD in a patient was shown to increase the risk of cardiac events after OLT significantly in three of six studies. The average prevalence of CAD was 14.4%. In predicting CAD, DSE had a composite sensitivity of 0.47 (95% CI, 0.32-0.62), specificity of 0.74 (95% CI, 0.68-0.79), PPV of 0.23 (95% CI, 0.15-0.33), and NPV of 0.89 (95% CI, 0.84-0.93). This review emphasizes the need to standardize cardiac risk stratification protocols to screen and prevent cardiac morbidity after OLT, standardize the definition of MACE to allow more uniform reporting, and the need for a safer but efficacious alternative to DSE in the evaluation of OLT candidates. ■

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MAIN POINTS

- Liver transplantation is the established treatment modality for patients with end-stage liver disease. Among patients undergoing orthotopic liver transplantation (OLT), cardiovascular disease is the leading cause of 30-day mortality.
- Dobutamine stress echocardiography (DSE) is frequently used as the initial screening test to evaluate cardiac risk factors prior to transplantation.
- The American Heart Association recommends invasive stress testing to be considered in liver transplantation candidates with no active cardiac conditions on the basis of the presence of multiple coronary artery disease (CAD) risk factors regardless of functional status.
- Multiple other modalities have been tested to screen for CAD before OLT. These include computed tomographic angiography and coronary calcium scoring, single-photon emission computed tomography, myocardial perfusion imaging, and cardiopulmonary exercise testing.
- Complications, such as arrhythmia and hypotension, occur after administration of dobutamine and atropine. The high complication rate stresses the need for a safer and more efficacious alternative to DSE.