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CLINICAL INVESTIGATIONS

Preoperative dobutamine stress echocardiography in patients undergoing orthotopic liver transplantation

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Background: Coronary artery disease (CAD) is associated with increased mortality in patients who undergo orthotopic liver transplantation (OLT). Chronic vasodilatory state and poor exercise tolerance in patients with end-stage liver disease make dobutamine stress echocardiography (DSE) preferred for preoperative evaluation of CAD prior to OLT. We studied the incidence of positive DSE results and the association between DSE results and perioperative and longer-term events.

Hypothesis: DSE results pre-OLT will predict short and long term outcomes.

Methods: We studied 460 patients who underwent DSE within 1 year prior to OLT between 2004 and 2011. Primary events included death and MI at 30 days post-OLT. We also recorded longer-term deaths.

Results: Four patients (0.9%) had an ischemic response to DSE, 360 (78%) were normal, and 96 (21%) were nondiagnostic. Fourteen patients (3%) had a primary event at 30 days following OLT (13 deaths and 1 NSTEMI), and there were 108 (24%) deaths at 4.6±2 years of follow-up. No patient with ischemia on DSE had a 30-day event. The accuracy, sensitivity, specificity, and positive and negative predictive values of DSE that was not normal (ie, ischemic or nondiagnostic response) to predict 30-day post-OLT events were 76%, 14%, 78%, 2%, and 97%, respectively. On Cox survival analysis, only baseline left ventricular ejection fraction (HR: 0.90, 95% CI: 0.85–0.96, $P < 0.001$) was associated with longer-term deaths.

Conclusions: Patients undergoing pre-OLT DSE have very low incidence of an ischemic response on DSE, and it has no association with 30-day events.

KEYWORDS

Dobutamine stress echocardiography, liver transplantation, outcomes

1 | INTRODUCTION

As orthotopic liver transplantation (OLT) outcomes improve, the criteria for candidacy have become more lenient to allow for consideration of an aging population with multiple comorbidities. It has been well established that cirrhotic patients with concomitant coronary artery disease (CAD) have worse posttransplantation outcomes than their counterparts, in large part due to the significant hemodynamic stress encountered perioperatively.[1–4] As such, there has been much interest in optimizing preoperative cardiovascular (CV) risk stratification for potential OLT recipients. Unfortunately, this remains one of the biggest challenges in the perioperative management of this patient cohort.

The classic hemodynamic changes seen in cirrhotic patients include increased cardiac output and chronotropic incompetence, attributed to the chronic vasodilatory state of these patients. This precludes the reliable use of nuclear single-photon emission computed tomography stress imaging to assess for CAD. Exercise stress testing is typically not feasible in these patients given their decompensated clinical status, which impedes an adequate exercise tolerance. By default, dobutamine stress echocardiography (DSE) gained popularity as the screening test for CAD in cirrhosis. However, the clinical utility

and accuracy of DSE in patients with end-stage liver disease is not well studied, and the results of available literature are conflicting. Although initial studies were optimistic about the role of DSE in diagnosing CAD,[5,6] more recent publications question its reliability for accurate diagnosis and risk stratification.[7–10] This controversy is reflected in the discordance between the current American College of Cardiology/American Heart Association (ACC/AHA) and American Association for the Study of Liver Disease guidelines (AASLD). Although ACC/AHA does not recommend routine noninvasive stress testing prior to OLT,[11,12] AASLD strongly advocates for the use of DSE as a screening tool in patients with any sort of cardiac risk factor.[13]

Clearly, further data are needed to definitively determine the utility of DSE within this patient cohort. In this study, we sought to better define the role of preoperative DSE by establishing whether there is an association between DSE results and clinical outcomes for patients undergoing OLT.

2 | METHODS

This was an observational single-center cohort study of 460 consecutive patients who underwent DSE within 1 year prior to OLT between 2004 and 2011. Institutional review board approval was obtained prior to data collection. All demographic and clinical data were entered prospectively at the time of initial encounter and were subsequently manually extracted for the purpose of the current study. We recorded individual demographics, medical history, severity of end-stage liver disease (based on the Model for End-Stage Liver Disease [MELD] score), medication use, test data, and postoperative events.

2.1 | Resting and dobutamine stress echocardiography

Standard echocardiographic machines (Philips Medical Systems, Andover, MA; GE Healthcare, Chicago, IL; and Siemens Healthineers, Erlangen, Germany) were utilized. Prior to the initiation of DSE, a comprehensive resting echocardiogram was performed according to American Society of Echocardiography (ASE) guidelines.[14] Standard valvular assessment (for stenosis and regurgitation) was performed using ASE guidelines.[15] Subsequently, DSE was performed by dedicated experienced personnel, under the supervision of the interpreting physician.[16] All patients were requested to hold β-blockers for 24 hours prior to the scheduled DSE.

Prior to initiating dobutamine infusion, standard resting echocardiographic images of the left ventricle (LV) were also obtained in short-axis and 2-, 3-, and 4-chamber views, to assess for wall-motion abnormalities. Resting electrocardiogram, heart rate, and blood pressure were recorded. Subsequently, dobutamine was infused continuously, starting at 10 μg/kg/min for 3 minutes and progressively increasing to 20, 30, and 40 μg/kg/min, until the patients achieved 85% of the maximum predicted heart rate (220 – age). If the target heart rate was not achieved, atropine was given, up to a total dose of 1 mg. At every 3 minutes, electrocardiogram, rhythm strip, heart rate, and blood pressure were recorded, along with symptoms. Also, at every stage, echocardiographic images of the LV were obtained in above-mentioned views. Similar echocardiographic data were also obtained at peak dobutamine infusion when the target heart rate was reached. Subsequently, ECG, rhythm strips, heart rate, and blood pressure were monitored during recovery for ≥6 minutes. All echocardiographic images were digitally stored, and DSE was interpreted by experienced cardiologists according to the standard recommendations of ASE.[16] An ischemic response during DSE was defined by new or worsening wall-motion abnormalities from baseline indicative of ischemia, whereas the absence of those findings was classified as negative study. The studies in which patients did not achieve the target heart rate were defined as nondiagnostic.

2.2 | Outcomes assessment

Primary outcomes included the incidence of death and nonfatal myocardial infarction (MI) at 30 days post-OLT. Secondary outcomes included long-term all-cause mortality. Cause of death was ascertained. Date of OLT was considered to be the date of initial follow-up, and the date of the last visit at our institution was considered to be the end of follow-up.

2.3 | Statistical analysis

Data were expressed as mean ±SD or median (interquartile range) for continuous variables and as frequency and percentage for categorical variables. To assess longer-term outcomes, Cox proportional hazards analysis was performed to test the association of various potential predictors with longer-term mortality. Hazard ratios (HR) with 95% confidence intervals (CI) were reported. Statistical analysis was performed with SPSS statistics, version 20.0 (IBM Corp., Armonk, NY). A P value of <0.05 was considered significant.

3 | RESULTS

Baseline characteristics of the study population are shown in Table 1. No patients had atrial fibrillation or CV symptoms at the time of DSE. The majority of the patients (70%) were male, and 68% had either hepatitis C virus or alcohol-related cirrhosis. As expected, the MELD score was high and the study population had an expected distribution of relatively low CV risk factors. The resting echocardiographic data are shown in Table 2. As expected, the majority of the patients (446 [97%]) had preserved left ventricular ejection fraction (LVEF; ≥55%), normal (or stage 1) diastolic dysfunction, normal LV dimensions, and nonsignificant valvular disease.

The relevant data at peak dobutamine infusion are also shown in Table 2. Of note, within the entire study population, 30% of patients needed additional atropine injection to increase the heart rate past the 85% maximal projected heart rate (MPHR) threshold. The majority (79%) achieved 85% of MPHR, whereas 21% had a nondiagnostic test due to not achieving 85% MPHR, despite the use of atropine at peak dobutamine infusion. In the nondiagnostic subgroup, the mean MPHR was 72% ±12% (range, 51%–84%). No patient in the nondiagnostic subgroup had an induced wall-motion abnormality. Of the 460 patients

TABLE 1 Baseline clinical characteristics of the study population (N = 460)

Variable	
Mean age, y	58 ±7
Male sex	324 (70)
Mean BSA, kg/m^2	2 ± 0.5
Etiology for liver transplantation	
HCV	187 (41)
Alcoholic cirrhosis	122 (27)
NASH	85 (18)
Others	66 (14)
MELD score	21 ± 3
HTN	161 (35)
DM	114 (25)
Hyperlipidemia	60 (13)
CAD	33 (7.0)
Smoking history	285 (62)
CKD	62 (14)
Stroke	9 (2.0)
Medications	
ASA	70 (15)
β-Blockers	281 (61)
Statins	29 (6.0)
ACEIs	82 (18)
INR	1.5 ± 0.5
Total bilirubin, mg/dL	6 ± 9
Serum Na, mg/dL	132 ± 6
sCr, mg/dL	1.5 ± 1.3

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ASA, acetylsalicylic acid (aspirin); BSA, body surface area; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; HCV, hepatitis C virus; HTN, hypertension; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease; Na, sodium; NASH, nonalcoholic steatohepatitis; sCr, serum creatinine; SD, standard deviation. Data are presented as n (%) or mean ± SD.

who underwent DSE within 1 year prior to OLT, only 4 (0.9%) had an ischemic response (3 of which were noticed in the right coronary artery and 1 in the left anterior descending coronary artery distribution), whereas 360 (78%) were normal (Table 2). No patient underwent cardiac catheterization during follow-up. No patient had a major CV event (death, MI, or sustained ventricular tachyarrhythmias requiring cardiopulmonary resuscitation or electrical cardioversion) at the time of dobutamine stress test. Fifteen (3%) patients had self-limiting arrhythmias (nonsustained ventricular tachycardia or atrial fibrillation) and 8 (1.7%) patients had an asymptomatic drop in systolic blood pressure during dobutamine infusion that resolved during the recovery period.

3.1 | Outcomes

Fourteen patients (3%) had a primary event at 30 days following OLT (13 deaths and 1 non–ST-segment elevation MI). The association between 30-day post-OLT events and DSE response (normal, nondiagnostic, or ischemic) is shown in Table 3. Of note, none of the patients with an ischemic response on DSE had a 30-day event; however, 2 patients with a nondiagnostic DSE had a 30-day event post OLT. The accuracy, sensitivity, specificity, and positive and negative predictive values of DSE that was not normal (ie, ischemic or nondiagnostic response) to predict 30-day post OLT events were 76%, 14%, 78%, 2%, and 97%, respectively. On the other hand, the accuracy, sensitivity, specificity, and positive and negative predictive values of DSE (ischemic vs normal + nondiagnostic response) to predict 30-day post-OLT events were 96%, 0%, 99%, 0%, and 97%, respectively. There were no perioperative strokes.

In terms of longer-term outcomes, there were 108 deaths (24%) at a mean follow-up of 4.6 ±2 years. In the current study population, the total mortality at 1, 3, and 5 years following OLT was 46 (10%),

TABLE 2 Resting and DSE characteristics of the study population

Resting echocardiographic data	
LVEF, %	58 ±4
Indexed LVESD, cm/m^2	1.5 ±0.2
Indexed LA area, cm/m^2	2.1 ±0.3
Moderate mitral regurgitation	5 (1.0)
Moderate aortic stenosis	5 (1.0)
Mitral valve E/e' ratio	8.2 ±3
Moderate tricuspid regurgitation	9 (2.0)
RVSP, mm Hg	30 ± 8
DSE data	
Resting heart rate, bpm	74 ± 13
Resting SBP, mm Hg	124 ± 21
% Maximum predicted heart rate achieved on DSE	84 ± 9
Peak achieved heart rate, bpm	135 ± 16
Peak achieved SBP, mm Hg	176 ± 16
Maximum RPP	18 489 ± 4007
Response to DSE	
Ischemic	4 (0.9)
Nondiagnostic (nonachievement of heart rate)	96 (21)
Normal	360 (78)

Abbreviations: DSE, dobutamine stress echocardiography; LA, left atrial; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; RPP, rate pressure product; RVSP, right ventricular systolic pressure; SBP, systolic blood pressure; SD, standard deviation. Data are presented as n (%) or mean ± SD.

TABLE 3 Association between 30-day events and response to DSE in the current study (N = 460)

	AEs 30 Days Post-OLT	No AEs 30 Days Post-OLT	Total
A: Ischemic and nondiagnostic response on DSE combined together			
Ischemic or nondiagnostic response on DSE	2 (true positive)	98 (false positive)	100
Negative DSE	12 (false negative)	348 (true negative)	360
B: Negative DSE and nondiagnostic response combined together			
Ischemic response on DSE	0 (true positive)	4 (false positive)	4
Negative or nondiagnostic DSE	14 (false negative)	442 (true negative)	456

Abbreviations: AE, adverse event; DSE, dobutamine stress echocardiography; OLT, orthotopic liver transplantation.

63 (14%), and 93 (20%), respectively. We subsequently performed Cox proportional hazard survival analysis in the study population to test the association of various relevant CV risk factors with longer-term mortality; the results are shown in Table 4. Other than resting LVEF, none of the known CV risk factors (clinical, resting echocardiographic, or DSE variables) were associated with longer-term mortality in the study sample. On the other hand, MELD score, as expected, was associated with longer-term mortality.

4 | DISCUSSION

The majority of current data has shown that DSE lacks the sensitivity to reliably screen OLT candidates for asymptomatic CAD.[7–10] However, it remains common practice to perform DSE as part of pre-OLT evaluation, even in patients with relatively low traditional cardiac risk factors. This may be due to the notion that DSE may be useful for perioperative CV risk stratification. The current study adds to the literature that highlights the limited role of DSE for both short- and long-term CV risk stratification of cirrhotic patients who undergo OLT. Also, it further validates the current opinion of the ACC/AHA guidelines in terms of not recommending preoperative DSE in patients being worked up for OLT.

TABLE 4 Cox proportional hazard analysis for long-term mortality in the current study

	Univariable		Multivariable	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age (for every 10-year increase)	1.20 (0.90–1.58)	0.21		
Sex	1.30 (0.83–2.02)	0.24		
HTN	1.19 (0.79–1.79)	0.39		
DM	1.15 (0.73–1.82)	0.56		
Hyperlipidemia	1.52 (0.66–3.51)	0.67		
CAD	1.43 (0.71–2.89)	0.30		
Smoking history	1.11 (0.62–1.89)	0.76		
sCr	1.03 (0.90–1.19)	0.65		
MELD score	1.14 (1.04–1.32)	<0.01	1.12 (1.03–1.35)	0.01
LVEF (for every 1% increase)	1.10 (1.04–1.16)	<0.001	1.09 (1.04–1.18)	<0.001
E/e' ratio	1.12 (0.76–1.66)	0.57		
RVSP (for every 10-mm Hg increase)	1.16 (0.87–1.55)	0.30		
% Maximum predicted heart rate achieved	1.02 (0.76–1.38)	0.89		
Maximum RPP	0.35 (0.06–2.13)	0.25		
LV response to dobutamine				
Normal	Ref			
Nondiagnostic	1.10 (0.70–1.75)	0.67		
Ischemic	1.25 (0.16–9.61)	0.83		

Abbreviations: CAD, coronary artery disease; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; HTN, hypertension; LV, left ventricular; LVEF, left ventricular ejection fraction; MELD, Model for End-Stage Liver Disease; Ref, reference; RPP, rate pressure product; RVSP, right ventricular systolic pressure; sCr, serum creatinine.

To our knowledge, this study includes one of the largest cohorts of cirrhotic patients who underwent DSE prior to OLT. Our results are consistent with prior studies and validate a high negative predictive value of DSE in predicting short-term CV outcomes, which has been the main pillar for those in favor of using DSE in this patient population.[7,9,17,18] However, the high negative predictive value is a false reassurance in this patient cohort. In our study, 86% of patients who had an adverse CV event at 30 days had a negative DSE prior to transplantation, whereas none of the patients with an ischemic DSE had an event at 30 days. These findings illustrate that a normal DSE does not inherently imply absence of obstructive CAD; and, more interesting, an ischemic DSE does not necessarily portend an increased perioperative risk of CV events. Essentially, DSE fails to effectively identify patients at increased risk for short-term CV events following OLT.

We found that the only CV variable that predicted increased long-term risk stratification in post-OLT patients was LVEF. Cirrhotic cardiomyopathy has become an increasingly recognized clinical entity and may explain the significance of LVEF in predicting long-term outcomes.[19,20] It is particularly important to recognize in OLT candidates that the hemodynamic stress imposed intraoperatively could precipitate acute exacerbations and, ultimately, cardiogenic shock. Myocardial strain imaging, which is a sensitive marker of LV function, may play important roles in prompt identification of these patients, which would allow for optimization of cardiac function prior to consideration of OLT. Further studies are needed to establish the role of these noninvasive imaging modalities in diagnosing cirrhotic cardiomyopathy and to further determine the clinical implications following OLT.

Contrary to the study performed by Umphrey et al.,[17] we did not find that peak rate pressure product or chronotropic incompetence were useful in identifying patients at increased risk for adverse long-term CV events. Their high prevalence of nondiagnostic studies at 37% (vs 21% in our study) may contribute to this difference. Our findings are significant in that they reiterate the lack of clinical correlation between the results of DSE and long-term outcomes. A resting echocardiogram may yield equivalent information regarding long-term prognostication from a CV standpoint.

The hemodynamic changes seen in cirrhotic patients portend unique challenges in establishing an optimal modality for noninvasive CV assessment. Due to lack of better options, DSE has remained the mainstay for screening and prognostication as part of OLT evaluation, but not without limitations, as we have described above. With advances in multimodality imaging, computed tomography angiography (CTA) may be a viable means for both screening and prognostication.[21] Cassagneau et al. found the results of CTA comparable with those of DSE, with 95% negative predictive value in 52 patients evaluated at a median of 18 months of follow-up.[22] CTA has additional benefits when compared with DSE, including the ability to define the patient's coronary anatomy and allowing for assessment of plaque burden, both of which may have significant implications in guiding anesthetic care. Further studies are needed to evaluate the accuracy of CTA in both diagnosing CAD and prognosticating CV risk for OLT

patients when compared with the gold standard, the coronary angiogram.

4.1 | Study limitations

As with any retrospective analysis, there is potential for an inherent selection bias. Our patient cohort carried a relatively low risk of CV disease, which is likely a reflection of the clinical approach for preoperative evaluation at our institution, in which high-risk patients are referred for coronary angiography. Our institution is well adept in OLT, and the results of this study may therefore not be generalizable across all surgical centers. There may be referral bias in that high-risk patients may not have been considered for OLT and therefore not included in the current study. For longer-term outcomes, we report all-cause as opposed to CV mortality, as it has been demonstrated previously that all-cause mortality is less biased than cardiac mortality.[23]

5 | CONCLUSION

Preoperative DSE for patients undergoing OLT does not appear to provide adequate diagnostic accuracy or incremental prognostic utility for short- or long-term outcomes following OLT. This strategy of risk stratification may need to be revisited in the current era of cost containment. It appears that instead of DSE, preoperative risk stratification should focus on traditional cardiac risk factors, and further investigation regarding the role of other imaging techniques is warranted for preoperative evaluation of intermediate-risk patients prior to OLT.

Author contributions

Krishna K. Patel, MD, and Laura Young, MD, are co–first authors with equal contribution to the work.

Conflicts of interest

The authors declare no potential conflicts of interest.

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