Cardiopulmonary Exercise Testing and Dobutamine Stress Echocardiography in Pre-Operative Assessment of Liver Transplant Patients

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Abstract: Orthotopic Liver Transplantation (OLT) is the established treatment for end-stage liver disease. Surgical procedures per se, with excessive bleeding, fluid shift, re-perfusion syndrome and electrolyte disturbances impose stress on the cardiovascular system. Patients with cardiac comorbidity undergoing OLT have higher perioperative morbidity and mortality. Cardiac assessment and optimisation are integral parts of the preoperative evaluation.

Different liver transplant (LT) centres have different pre-assessment policies, but in general, all centres are moving towards more structured and objective pre-assessment. Dobutamine Stress Echocardiography (DSE) and Cardiopulmonary Exercise Testing (CPEX) are useful tools in preoperative risk assessment and patient optimization. With time, we will also learn more about their limitations.

In this paper, we reviewed the literature on the value of DSE and CPEX for preoperative risk assessment and preoperative optimization of liver LT patients. We also added our high-volume LT centre experience.

Current literature and our experience suggest that the DSE test, used widely as a non-invasive procedure to detect patients with coronary artery disease, is not as sensitive and specific as we would have expected. It is currently being used primarily for its negative predictive value. DSE has been gradually replaced with a completely different test that measures functional capacity and the ability to cope with increasing demands during the perioperative and postoperative periods. Because CPEX is comprised of several components and its interpretation is complex, anaerobic threshold (AT) was a good component to start with. Although there is evidence that lower AT is associated with higher morbidity, intra-hospital stay and mortality, further investigation is needed in order to clarify its value in LT patient pre-assessments.

Keywords: Liver transplantation, Stress echocardiography, Cardiopulmonary exercise test, Pre-assessment.

INTRODUCTION

Orthotopic Liver Transplantation (OLT) is the established treatment for end-stage liver disease. Surgical procedures per se, with excessive bleeding, fluid shift, re-perfusion syndrome and electrolyte disturbances impose stress on the cardiovascular system. Cardiovascular complications are the second most common cause of postoperative morbidity and mortality [1]. Patients with cardiac comorbidity undergoing OLT have higher perioperative morbidity and mortality. Cardiac assessment and optimisation are integral parts of the preoperative evaluation.

Apart from routine screening transthoracic echocardiography, there are no specific recommendations for cardiovascular assessment in liver transplant (LT) patients with increased risk of cardiovascular comorbidity. Different centres have varying protocols for cardiac risk stratification.

Dobutamine Stress Echocardiography (DSE), where pharmacologically induced stress similar to intraoperative stress during LT is used to assess the functional capacity of the coronary vessels, has been widely used for identifying patients with increased risk of ishaemic cardiac event intra- and postoperatively during LT. However, DSE is losing its popularity, although it is still the preferred method of preoperative risk assessment in some LT units. Indications for DSE are significantly reduced, and we will explain the reasons for this later in this paper.

Over the last decade, Cardio-Pulmonary Exercise Testing (CPEX) has become increasingly popular in preoperative cardiorespiratory risk assessment for all types of surgery, including LT. Some LT centres expose patients to CPEX only if they have increased cardiorespiratory risk; others perform CPEX routinely in every LT candidate. The studies evaluating the value of CPEX in cardiopulmonary risk assessment for LT patients are adding to our knowledge of CPEX advantages and limitations. Due to limited number of LT operations (up to 200 per year in high volume centres and up to 50 per year in low volume LT centres) collaborative long term work between centres is required in order to drew meaningful conclusions.

This is the first article to compare the value of DSE and CPEX for pre-assessment of LT patients. In this article, we will review current knowledge on the value

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of CPEX and DSE tests in preoperative stress evaluation of LT candidates and add our centre's experience.

MATHERIAL AND METHODS

We searched for published studies using computerized bibliography search and hand searched within relevant articles bibliographies. For our search in PubMed , we used MeSH headings "stress echocardiography" and "liver transplant" and "cardiopulmonary exercise test" and "liver transplant". We considered articles between 1975 and November 2013, written or translated to English language. A total of 13 articles was found by two reviewers. For DSE studies, we assessed the type of study, sensitivity, specificity, positive and negative predictive values. For CPEX studies, we assessed the design of study and critically analysed results.

RESULTS

Dobutamine Stress Echocardiography (DSE) in Liver Transplant Surgery

DSE is an established non-invasive pharmacological method that is used to detect and assess the severity of myocardial ischemia in patients with known or suspected coronary artery disease (CAD). It is also valuable in the detection of myocardial viability.

According to the protocol, Dobutamine infusion is gradually increased while echocardiography is performed, and the endpoints under consideration are regional wall motion abnormalities induced pharmacologically, increase in end systolic volume, reaching the target heart rate or occurrence of severe complications [2, 3].

Studies in non-cardiac surgery patients have shown that DSE provides prognostic information predictive of perioperative cardiac complications [4].

However, DSE has a high rate of inconclusive tests in patients with end-stage liver disease [5]. This is due to the failure to achieve the target heart rate or inadequate heart rate responses that are the result of frequent use of beta-blockers to control portal hypertension. Cirrhotic cardiomyopathy can also contribute to these inconclusive tests as it can cause chronotropic incompetence [6].

There are eight studies, presented in Table **1**, have evaluated the usefulness of DSE in liver transplant patients.

Recent quantitative systematic reviews assessing DSE's use in detecting coronary artery disease (CAD) and predicting perioperative and long-term cardiac events in patients undergoing OLT revealed accuracy for CAD that included a sensitivity of 0.32, specificity of 0.78, positive predictive value (PPV) of 0.37 and negative predictive value (NPV) of 0.75. Accuracy for prediction of perioperative hard (myocardial infarction, cardiac death, cardiac arrest, and asystole) and soft (other) cardiac events was a sensitivity of 0.2 and 0, specificity of 0.99 and 0.99, PPV of 0.33 and 0, and NPV of 0.98 and 0.89, respectively. For long-term hard

Table 1: Dobutamine Stress Echo Test as Diagnostic Criteria for Coronary Artery Disease and Predictor of Major Cardiovascular Events During Liver Transplantation

Study	Year	Type/ No	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Donovan [2]	1996	Pro / 165	88	33		
Plotkin [7]	1998	Pro/ 80	100	90	33	100
Williams [3]	2000	Pro / 121	Poor	Poor	Poor	86
Findlay [8]	2005	Pro / 119	20	90	Low	High
Umphrey [5]	2008	Ret / 284 Peak Rate Pressure Product <16 332	Increased risk if unable to achieve >81% target HR			96
Harinstein [9]	2008	Ret / 105	17	88	44	64
Safadi [10]	2009	Ret / 413	Low	95	Low	>90
Rudzinski [11]	2011	Ret/298	Modified HR reserve index is predictor of chronotropic incompetence			

Pro-prospective; Ret-retrospective, PPV-Positive predictive value, NPV-Negative predictive value.

and soft cardiac events, sensitivity was 0.5 and 0, specificity was 0.99 and 0.98, PPV was 0.33 and 0, and NPV was 0.99 and 0.96, respectively [12]. This review article has demonstrated what has already been made obvious in previous studies: that DSE has limited accuracy for the detection of CAD for OLT. The main strength of DSE is its high negative predictive value for both perioperative and long-term cardiac events. Therefore, the DSE test that has been used in the past for cardiac risk assessment for OLT patients has been gradually phased out. There are rare clinical situations where DSE is recommended because of its negative predictive value and relative non-invasiveness. There have been some attempts to use risk index calculations [11] as a predictor of intra- and postoperative risks for cardiovascular events, derived from DSE measurements, but they need to be evaluated in the future.

Cardiopulmonary Exercise Testing (CPEX) in Liver Transplant Surgery

This relatively simple-to-perform test has gained popularity in pre-assessment of surgical patients. CPEX provides a combined assessment of cardiac, pulmonary and circulatory function. CPEX provides diagnostic and prognostic information in patients with cardio-respiratory impairment.

Cardiopulmonary exercise testing is conducted using a bicycle ergometer along with heart rate, blood pressure, oxygen saturation and ECG monitoring and breath-to-breath gas analysis. The exercise protocol is standardized and includes a period of 2-3 minutes of acclimatization to the equipment, followed by freewheeling for 2 minutes. Assessment of exercise capacity is typically performed on a motorized treadmill or a stationary cycle ergometer. Electrocardiography, non-invasive blood pressure, pulse oximetry and gas analysis monitoring are performed during the test. Several parameters are derived from CPEX. The most important variables are peak and maximal oxygen consumption (VO2), anaerobic threshold (AT) and ventilatory efficiency (VE/VCO2).

The aim of cardiopulmonary exercise testing in the preoperative setting is to objectively assess the body's response to 'stress' by graded, exercise-induced increases in oxidative demand. This, in turn, is purported to mimic the perioperative 'stress' on the respiratory and metabolic reserves of the individual, and is used to provide information on the individual's ability to cope with these increasing demands. CPEX can help to stratify risk, optimise patients preoperatively and plan appropriate post-operative care and management.

The most commonly studied data derived from cardiopulmonary testing to predict perioperative morbidity is the anaerobic threshold [13].

CPEX is considered a safe test and major complications are rare. Major complications during CPEX are reported to occur in the range of 0-5 per 10,000 and death <5 per 100,000 [14,15] CPEX should be performed where adequate resuscitation facilities are available.

Several studies in major non-cardiac surgery have shown that CPEX can predict when patients are at increased risk of post-operative complications.

Patients with end-stage liver disease awaiting OLT have poor exercise capacity and reduced cardiopulmonary reserve.

Table 2. Cardiopulmonary Exercise Test as Predictor of Major Cardiovascular Events in Liver Transplant Surgery

Study	Design	No. of Patients Studied	Conclusion
Epstein *et al*. 2004 [16]	Not stated	156	Peak VO_2 < 60% and VO_2-AT < 50% had mortality of 36% (p < 0.01)
Dharancy *et al*. 2008 [17]	Retrospective	135	Peak VO2 < 60% had higher length of hospital stay and mortality (Sensitivity 90.7%, Specificity 83.3%)
Prentis *et al*. 2012 [18]	Prospective	182	84% survivors at 90 days (Mean AT-12.1ml/kg/min) Non-survivors (Mean AT-7.9ml/kg/min) AT > 9.6ml/kg/min had 100% PPV Sensitivity 87% Specificity 100%
Bernal *et al*. 2013 [19]	Retrospective	223	One year post LT survivors had higher anaerobic threshold than non-survivors

CPEX has been increasingly used as a preoperative assessment tool for these patients. Reduced peak VO_2 < 60% during CPEX as shown by Epstein *et al*. [16] and Dharancy *et al*. [17] in liver transplant patients is associated with higher short-term mortality and increased hospital stay (Table **2**).

Prentis *et al*. [18] have used AT as the main CPEX variable as AT is said to be reliable, repeatable and patient specific [18]. They have demonstrated that AT > 9.6ml/kg/min has 100% PPV for survival.

The most recent study from King's College hospital has confirmed that patients with a higher anaerobic threshold have a higher survival at least one year after LT [19].

Our clinical experience is that, when performed regularly on all LT candidates, CPEX can detect patients with an increased preoperative risk of intra- and postoperative cardiac and other complications and increased mortality risk. It can indicate the need for other diagnostic procedures, such as coronary angiography, right heart studies, or other diagnostic tests. CPEX can be used together with other diagnostic tests to help optimize patients for OLT or to detect patients who are too high-risk for OLT. Patients with unexpectedly poor performance during CPEX, if no other risk factors are present, can be asked to repeat CPEX. Some patients with poor performance can be advised to increase physical activity or lose weight and then repeat CPEX several months later and check whether increased physical activity contributed to better performance.

Anaerobic threshold is not a magic number that will stratify risk and predict all postoperative events, as there are other factors contributing to outcome, such as quality of transplanted liver, surgical and anaesthetic technique and experience, Intensive Care quality etc.

RESULTS AND DISCUSSION

Liver transplantation is a complex surgical procedure in which multiple factors influence the outcome. These factors include: patient's preoperative status, quality of donor's liver, transplant centre's experience (including the volume of transplant centre), and the multidisciplinary team's experience. Preoperative assessment is only one factor, but it is a very important component that can influence the outcome. Preoperative assessment has changed from a subjective into a more objective process. Every component of that process is important and can contribute to an improved outcome for each individual patient, as well as to outcomes for the LT patient population as a whole.

Different LT centres have different pre-assessment policies, but in general, all centres are moving towards more structured and objective pre-assessment. DSE and CPEX are useful tools in preoperative risk assessment and patient optimization. With time, we will also learn more about their limitations. For example, the DSE test, used widely as a non-invasive procedure to detect patients with coronary artery disease, is not as sensitive and specific as we would have expected. It is currently being used mainly for its negative predictive value. DSE has been replaced with a completely different test that measures functional capacity and ability to cope with increasing demands during the perioperative and postoperative periods. CPEX is comprised of several components and its interpretation is complex, so for everyday practice and as a starting point, we use anaerobic threshold. Although there is evidence that lower AT is associated with higher morbidity, intra-hospital stay and mortality, further investigation is needed in order to clarify its value in LT patient pre-assessments. Further studies may substantiate the findings and make CPEX a useful tool for improving the allocation of organs to appropriate recipients.

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