Combined Cardiac Surgery and Liver Transplantation: Three Decades of Worldwide Results

Alexandros Giakoustidis[1], Thomas P. Cherian[2], Nikolaos Antoniadis[1], Dimitrios Giakoustidis[1]

1) Department of Transplant Surgery, Medical School, Aristotle University and Hippokration General Hospital, Thessaloniki, Greece; 2) Institute of Liver Studies, King's College Hospital, London, United Kingdom

Abstract

Background: Patients with end-stage-liver-disease (ESLD) require orthotopic liver transplantation (OLT) as treatment. However, cirrhotic cardiomyopathy can be clinically revealed during OLT, with the possible development of a transient overt congestive heart failure. A number of patients require a combined procedure of liver transplantation and heart surgery, which includes heart transplantation, aortic valve replacement or coronary artery bypass grafting. Indications for combined liver-heart transplantation include heart failure with associated cardiac cirrhosis, familial amyloidosis, familial hypercholesterolemia and hemochromatosis, and homozygous β-thalassemia. **Methods/ Results**. We performed a thorough research of Pubmed/ Medline, gathering and discussing data concerning this clinical condition and its treatment. **Conclusion**: In patients with end-stage liver disease, who are unable to tolerate an OLT post-operatively due to cardiac dysfunction, combined cardiac surgery and OLT appears to have certain advantages.

Key words

Combined – heart – liver – transplantation – cardiac surgery.

Abbreviations

ESLD: end-stage-liver-disease; OLT: orthotopic liver transplantation; OHT: orthotopic heart transplantation; CAD: coronary artery disease; CHLT: combined heart-liver transplantation; PBC: primary biliary cirrhosis; CPB: cardiopulmonary bypass; PTCA: percutaneous transluminal coronary angioplasty; CAGB: coronary artery bypass grafting; AVR: aortic valve replacement; FAP: familial amyloidotic polyneuropathy.

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Address for correspondence: Dr Alexandros Giakoustidis
Department of Transplant Surgery
Medical School, Aristotle University
Hippokration General Hospital
Thessaloniki, Greece
Email:alexgiakoustidis@gmail.com

Introduction

Although a few decades ago heart disease was considered a rare entity in cirrhotic liver patients, it is now clear that transplantation in patients with end stage liver disease (ESLD) can often be followed by cardiovascular complications, including acute coronary occlusion, arrhythmias and congestive heart failure [1-3].

While portal hypertension has been documented to initiate systemic vasoconstriction, contributing to underlying renal insufficiency and the hepatopulmonary syndrome, with pulmonary vascular shunting and hypoxia [4], Lee et al introduced the clinical entity named cirrhotic cardiomyopathy, which describes chronic cardiac dysfunction in patients with liver cirrhosis, including a sustained peripheral vasodilation resulting in a hyperdynamic circulation with a high cardiac output and eventually a sustained reduction in cardiac afterload and increased cardiac output [5-8].

Patients with ESLD require orthotopic liver transplantation (OLT) as treatment. Adequate heart performance is very important in patients undergoing OLT, since it involves a major surgical technique and an increased inflammatory load inducing severe stress to the cardiovascular system. Cirrhotic cardiomyopathy can be clinically revealed during OLT, with the possible development of transient overt congestive heart failure. This deteriorating cardiac function appears to be temporary in many cases, with the hyperdynamic circulation reversing in the period following OLT [9-11].

A number of patients require a combined procedure of liver transplantation and heart surgery, which includes heart transplantation, aortic valve replacement or coronary artery bypass grafting. Indications for combined heart-liver transplantation (CHLT) include heart failure with associated cardiac cirrhosis, familial amyloidosis, familial hypercholesterolemia and hemochromatosis and homozygous β-thalassemia [12]. Additionally, patients with end-stage

liver disease and coronary artery disease (CAD) have been reported with simultaneous liver transplantation and coronary artery bypass grafting [13].

Severe valvular heart disease can be encountered in patients with ESLD, but without requiring orthotopic heart transplantation (OHT). In other cases valve repair or replacement secondary to bacterial endocarditis has been performed secondary to OLT [14-16]. However, patients with significant aortic stenosis and ESLD have been reported who have undergone a combined aortic valve replacement (AVR) and liver transplantation because the surgical intervention to the heart was considered essential [17].

Combined heart-liver transplantation

While OLT is considered the gold standard treatment for patients with advanced liver disease, unresectable non-metastatic hepatocellular carcinoma, or certain metabolic diseases, OHT is the therapeutic approach to highly symptomatic patients with end-stage heart failure and at an increased risk of death [18]. Liver abnormalities, or significant cardiac dysfunction which may be revealed during pre-transplant evaluation of candidates for solid-organ transplantation, and also a known advanced liver disease in OHT candidates, or severe heart disease in OLT candidates, could all result in these patients being denied OHT or OLT in several transplant centres, because of the increased risk of peri-operative morbidity and potential mortality. These patients, and also the ones with certain metabolic diseases, would benefit from CHLT, as long as they were evaluated as acceptable candidates for this procedure. Additionally, patients undergoing OLT would benefit by a concomitant cardiac procedure.

The first report of a successful CHLT was reported in 1984 by Starzl et al on a 6-year old girl with familial hypercholesterolemia and coronary artery disease [19]. The survival at time of publication was 10 weeks and there were no serious complications reported until then, with the child eventually dying at the age of 13. Shaw et al from the same institution reported two more cases of CHLT a year later, one for familial hypercholesterolemia and coronary artery disease and the second for biliary hypoplasia and cardiomyopathy, without good results though, and both patients dying during admission. The unsuccessful outcome was attributed then to the importance of the size of the donor organs and the compromise made for a combined procedure. They did suggest, however, a possible immunological advantage to transplanting two organs in combination from the same donor [20].

In 1987, Wallwork et al reported a heart-lung-liver transplantation on a patient with end-stage primary biliary cirrhosis, pulmonary hypertension and cardiorespiratory failure with encouraging results [21]. Since then authors from several institutions have published their experience on CHLT indicating an increase in patient survival and a decline in graft rejection throughout the years. Rela et al in 1995 reported 37 liver transplantations on patients with liver-based metabolic disorders, with two patients receiving CHLT. The first presented with familial hypercholesterolemia and coronary artery disease and the second with familial amyloidoidotic polyneuropathy (FAP) and congestive heart failure, with survival at time of publication at 3.7 years and 1.7 years respectively [22].

Heart-lung-liver transplantations appear to demonstrate several complications according to Dennis et al, who reported a series of 4 patients in 1996. Complications included mainly early pulmonary rejection and reoperation for intrathoracic bleeding the first post-operative day, with one death on the 15th day post-operatively. Nevertheless, survival until time of publication ranged from 20 months to 100 months [23].

Several authors in the 1990s reported good results for CHLT in case reports and small case series with patients suffering from hepatic and cardiac failure, and with a survival until time of publication ranging from 9 months up to 100 months [24-29], highlighting careful selection of patients among other factors, and also the challenges in the post-operative period with high incidence of renal failure, a need for delicate fluid regulation, physiologic pressure sensitivity and good coordination of both surgical teams.

The experience of CHLT on four adults with FAP was reported by Nardo et al, with normal cardiac performance and disease free survival up to 40 months following transplantation for the two out of four patients transplanted, highlighting the importance of preoperative clinical condition and the possible positive effect of venovenous bypass during CHLT [30]. The effect of preoperative clinical condition of candidates on postoperative outcome was pointed out also by Pilato et al, who reported their institution's experience of CHLT on five patients with FAPNMet30 [31]. They concluded by emphasizing the important distinction of the two forms of FAP, Met30 and NMet30, as was proposed earlier by Stangou et al, stating the value of CHLT as a therapeutic option for patients with FAPNMet30 [32].

With reports of 1-year survival rates for CHLT, reaching 80% in the late 1990s [28], but with a great percent of patients listed for this dual procedure not surviving until transplantation, Porrett et al emphasized in 2004 the critical subject of more precise criteria for patient selection [33]. The authors reported the results from a retrospective data review on patients listed for CHLT from both their institution and their national UNOS registry, with 33 CHLTs having been performed until that time. They indicated that survival until transplantation was associated with less severe hepatic disease, questioning though the efficacy of the MELD system to accurately predict the mortality of patients with liver failure and concomitant severe cardiac dysfunction.

The issue of MELD's efficacy for the waiting list of patients for CHLT was also raised by Faenza et al, with evaluation indices of cardiac pathology characterised as misleading [34]. The authors also highlighted the fact that MELD does not include criteria which appear to be strongly associated with patients' survival, such as nutritional and infection status. In 2007, Barshes et al reported results concerning 36 patients with CHLT from January 1998

until November 2005 in the USA, according to the UNOS Registry and published literature [12]. After performing a Kaplan-Meier survival analysis of the available data, a 84% one-year and 74% three year post-transplant patient survival was demonstrated. The authors also described the most common indications for CHLT, including FAP and heart failure associated with cardiac cirrhosis among others. The importance of OHT being performed first before OLT was also highlighted, because of low tolerance of a heart with end-stage injury to the hemodynamic changes seen during OLT. Veno-venous bypass was proposed for maintaining preload during OLT, although cardiopulmonary bypass (CPB) would not be a problem in patients with structurally normal livers, as in FAP or familial hypercholesterolemia. 'Piggyback' liver transplantation was also proposed as effective in maintaining cardiac output. On the other hand, Bernier et al described CHLT with CPB on a patient with right heart failure and ESLD, as a valuable option [35]. They noted that the patients did not experience any renal dysfunction post-operatively and that the reperfusion time offered a period of hemodynamic stability, necessary for the implantation of the liver at the same time. However, these conclusions are based on one single case report.

Te et al also reported their analysis on the data from CHLT performed in the USA, including the heart-liver-kidney transplantations, demonstrating 1- and 3-year patient survival rates at 84.8% and 79.5% respectively, which were higher that the ones reported by Barshes et al previously [18]. The authors highlighted the fact that these survival rates were different to the ones of single heart or liver transplantation, including the fact that the CHLT recipients from their study were able to maintain a good graft function with less immunosuppresion when compared with patients receiving OHT or only kidney transplantation. They also showed that liver and heart graft rejections were low, at 10% and 13% respectively, in spite of the low immunosuppression levels.

In 2009, Raichlin et al published their institution's results concerning CHLT on a large cohort of 15 patients [36]. They reported patient survival rates with receiving CHLT equivalent to their patients that had undergone isolated heart or liver transplantation. They were also in agreement with published reports from other centres, whereby acute tubular necrosis complicates the early post operative period of many patients. They also noted that liver graft rejection was infrequent and heart graft rejection was less frequent than in isolated heart transplantations. Most of their patients received CHLT for FAP with excellent results as reported by other authors [37], but this was also the case for patients with end-stage liver and cardiac disease (Table I).

Coronary artery bypass grafting and liver transplantation

Patients with CAD are considered a high-risk group for OLT. Plotkin et al reported back in 1996, a 3-year mortality rate of 50% for a group of 32 patients with known CAD undergoing OLT [38]. This resulted in a more focused pre-transplant screening of patients for CAD, with greater utilization in percutaneous revascularization procedures and also changes in patients' medical therapy [39]. Diedrich et al in 2008 published the results of a retrospective cohort of 42 patients with known CAD undergoing OLT, compared with a control group of 42 patients without CAD who also underwent OLT at the same institution, the same period and who were matched for gender, age and primary liver disease [40] (Table II). They reported that postoperative mortality was more frequent at 1 and 3 years in the CAD than the control group. Additionally, they observed an overall 3-year mortality of 26% and morbidity of 38%, whereby the cases reported by Plotkin et al a decade before were 50% and 80%, respectively. However, they could not demonstrate whether the hugely improved outcome was due to improved management of CAD among the OLT population or to a more careful patient selection, with subsequent denial to transplantation of high risk patients.

Percutaneous transluminal coronary angioplasty (PTCA) can often be performed prior to the OLT, in patients with hepatic and coronary artery disease. However, there are cases when lesions are not amenable to PTCA, but also coronary artery bypass grafting (CABG) cannot be performed prior to OLT, because an advanced but stable liver disease could rapidly progress to hepatic deterioration after general anaesthesia and CPB. In such cases combined CABG and OLT were performed. From 1995 until 2004 only a few case reports, and one report of two cases of combined CABG-OLT were published, with survival rates ranging from 6 to 14 months postoperatively at time of publication, one intraoperative death and complications following this dual procedure, including renal failure, massive blood loss, myocardial dysfunction and wound infection among others [41-43].

In 2004, Axelrod et al published their institute's results on five patients having undergone combined CABG-OLT [44]. They reported a 1-year survival of 80% with no perioperative death. They emphasized that the main indication for a combined procedure is the presence of significant, high-risk coronary lesions with preserved left ventricular function and severe liver disease, while the majority of their five patients reported had Child-Turcotte-Pugh class C cirrhosis, in which case CABG without transplant was precluded, and one patient had compensated cirrhosis and hepatocellular carcinoma. They also highlighted the careful donor selection and the use of continuous transesophageal echocardiography (TEE), which facilitated the patients' course on CPB and during OLT, and placement of all patients on veno-venous bypass during OLT for maximum hemodynamic stability. The patients' survival rates ranged from 10 to 43 months until time of publication, with one death 2.5 months post operatively and complications including cardiac arrest, pericardial effusion and acute rejection. Lebbinck et al reported a case of CABG and OLT with off-pump CPB, describing it as a good option in selected patients with combined CAD and ESLD (Child C), and for those who are in need of liver transplantation and coronary revascularisation [45].

Table I. Combined heart-liver and heart-lung-liver transplants

Date	Authors [Ref]	n	Age (years)	Sex	Pathology liver/ Pathology heart	Reported complications	Survival at time of publication
1984	Starzl et al [19]	1	6	F	FHCH/CAD	None	10 weeks
1985	Steed et al [46]	2	NA	NA	NA	NA	NA
1985	Shaw et al [20]	3	2-17	3F	FHCH/CAD, BH/ Cardiomyopathy,	Postop organ failure (heart and liver), MI	2 deaths during admission, 1 year
1987	Fricker et al [47]	2	2- 6	2F	FHCH/CAD, BA/ Dilated cardiomyopathy	Hypertension, Acute organ failure	1 death, 2 years
1990	Bahnson et al [25]	3	2- 17		FHCH/CAD (2), BH/ Congestive heart failure	N/A	2 deaths, 5 years
1995	Rela et al [22]	2	33- 61		FHCH/CAD, FAP/ Congestive heart failure		3.7 years, 1.7 years
1996	Dennis et al [23]	4	21-35	2M, 2F	CF(3), PBC/ Plexogenic pulmonary hypertension	Early pulmonary rejection, pneumonia, intrathoracic bleeding	1 deaths, 20 months, 50 months, 100 months
1999	Befeler et al [28]	3	39- 47	2 M, 1 F	ALD/ DCM (2), CLD/ ICM	Renal failure, acute cellular rejection of liver	1, 3, 4 years
1999	Tazbir et al [29]	3	39-47		ALD/ Congestive heart failure (2), CLD/ Congestive heart failure	None	4 months, 2 years, 2.3 years
2004	Nardo et al [30]	4	NA	4M	FAP	Postoperative bleeding, renal failure, sepsis, heart failure, intestinal ischemia	1 month, 42 months, died after 2 months, died after 20 months
2004	Porrett et al [33]	3	NA	2F-1M	Ischemic CM,CLD, DCM, Congenital, HCV	Brain death following surgical technical complication	1 death, 7 years, 3 years
2006	Faenza et al [34]	6			(5) FAP, (1) HCV cirrhosis, DCM		4 alive until publication, 2 deaths
2007	Pilato et al [31]	5			FAPN Met30		3 alive until publication, 2 deaths (1 20 months survival)
2007	Barshes et al [12]						1y&5y SR 88% and 78%, respectively..
2008	Te et al [18]				amyloidosis (30%).		1y&5y SR 84.8%, and 75.6%, respectively.
2009	Raichlin et al [36]	15			familial amyloidosis (11), hemochromatosis (1), restrictive cardiomyopathy and cardiac cirrhosis (1)		1y&5y SR 100%, 75% respectively
2010	Hennessey et al [48]	4	48- 57	4 M	FHCM, HRCM, right heart failure and congestive cirrhosis, HBV cirrhosis		all patients remaining well 25-38 months post-operatively

Abbreviations: FHCH: Familial hypercholesterolaimia; CAD: Coronary artery disease; BH: Biliary hypolasia; BA: Biliary atresia; FAP: Familial amyloidotic polyneuropathy; CF: Cystic fibrosis; PBC: Primary biliary cirrhosis; ALD: Alcoholic liver disease; DCM: Dilated cardiomyopathy; CLD: Cryptogenic liver disease; ICM: Idiopathic cardiomyopathy; FHCM: familial hypertrophic cardiomyopathy; HRCM: hypertrophic restrictive cardiomyopathy; NA: not available; SR: survival.

Aortic valve replacement and liver transplantation

Patients with ESLD, occasionally also have severe valvular heart disease, which does not require OHT. Parker et al reported in 2001 the first simultaneous AVR with OLT, with AVRs following OLR for bacterial endocarditis or aortic stenosis, having been presented previously by other authors [17]. The dual procedure was performed on a 56-year old man with ESLD, whose left ventricular function was well preserved during progression of aortic stenosis until just before surgery, when he presented with congestive heart failure, but without evidence of CAD. Patient's survival was 30 days to time of publication and a reversible brachial plexus injury was reported. In 2003, Tzakis' group reported a case of simultaneous AVR and liver transplantation, with the patient developing an intracaval thrombus of the graft liver and subsequent pulmonary embolism [49]. The authors highlighted the possibility of this complication occurring because of the piggyback technique they used, and the patient had great bleeding due to severe coagulopathy and

Table II. Coronary artery bypass grafting (CABG) and liver transplantation (OLT)

Date	Reference	n	Age (years)	Sex	Liver disease	Reported complications	Survival at time of publication
1995	Morris et al [50]	1	61	M	HCV cirrhosis	Atelectasis requiring intubation, renal failure requiring long term dialysis, CVA, at 6 months bedridden and aphasic	6 months
1996	Manas et al [42]	1	56		ALD	None	1 year
1996	Plotkin et al [38]	2			NA	Massive blood loss (>50 units), myocardial dysfunction after weaning	1 died intraoperatively
1998	Massad et al [43]	1	58	M	Hepatitis C& HCC	Wound infection at site of LSV harvest treated with antibiotics	1 year
2003	Kniepeiss et al [23]	1	47	M	Hepatitis B	None	14 months
2004	Axelrod et al [44]	5	48-66	4 M, 1 F	Hepatitis C, ALD, NASH, Polycystic liver disease	Pericardial effusion requiring pericardial window, recurrent hep C and liver failure, cardiac arrest, nosocomial pneumonia, acute rejection	2,5- 43 months
2010	DeStefano et al [51]	5	60- 68	5 M	ALD, NASH, HCC, CLD	Atrial fibrillation, fluid in pleural space, hypotension, cardiac tamponade, coagulopathy, atrial fibrillation, acute renal failure, acute respiratory failure	1 death unrelated to a coronary event

PVT: portal vein thrombosis; NASH: non alcoholic steatohepatitis; HCV: hepatitis C virus; HCC; hepatocelular carcinoma; ALD: alcoholic liver disease; CLD: cryptogenic liver disease; CVA: cardiovascular accident; LSV: lesser saphenous vein

fibrinolysis during the procedure, without being on veno-venous bypass or receiving antifibrinolytic drugs.

It should also be noted that in 2001, Eckhoff et al described a combined procedure involving aortic valve replacement, coronary artery bypass surgery and OLT, on a 63-year old man with cirrhosis secondary to hepatitis C and concomitant severe aortic stenosis and coronary disease, with patient's survival of 2 years at time of publication [52]. On the other hand, Sieders et al presented in 2010 the hazardous situation that sequential AVR and liver transplantation can result in, despite advances in anaesthesiological and surgical techniques. Clotting disturbances proved to have fatal consequences in one patient, and a good post-operative outcome was noted in the second of a total of two patients [53].

Summary and conclusions

One can understand from a review of the published data on CHLT and other cardiac surgery combined with liver transplantation, that results have improved greatly throughout the last three decades. Especially in the most recent decade there has been a clear improvement in patient survival, due to advances in surgical techniques and immunosuppressive agents among others. However, one can not compare outcome results of patients receiving CHLT, compared to patients undergoing OLT combined with some form of cardiac surgery; each case has to be reviewed individually. In CHLT, the liver, as in combined liver kidney transplantation in humans, seems to offer protection to the implanted heart. Definitely a more careful selection of

Table III. Aortic valve replacement (AVR) and liver transplantation (OLT)

Date	Reference	n	Age	Sex	Pathology	Reported complications	Survival at time of publication
2001	Parker et al [17]	1	56	M	Laennec's cirrhosis and AS	Reversible brachial plexus injury	30 days
2003	Nishida et al [46]	1	49	M	Hepatitis C and Laennec's cirrhosis, aortic stenosis	Pulmonary embolism, reoperation for biliary reconstruction, generalised seizure	3 months
2010	Sieders et al [48]	2				Clotting disturbances, massive lung embolism	14 months, 1 death
2010	DeStefano et al [49]	4	47-66	4 F	Alcohol, PBC, PBC & autoimmune hepatitis, cryptogenic cirrhosis	Atrial fibrillation, acute respiratory failure, acute delirium, hypotension, cardiogenic shock, lactic acidosis	1 death

PBC: primary biliary cirrhosis; AS: aortic stenosis

patients awaiting CHLT has improved the post-transplant results, although the system of categorising the patients in the waiting list for this dual procedure is accumulating much scepticism.

On the other hand, CHLT is accompanied by a number of complications, and especially in the first years of its application, resulted in great mortality and morbidity. Apart from the intraoperative challenges it offers, both from a surgical and an anaesthetic point of view, acute tubular necrosis is a frequent early postoperative complication of CHLT, resulting from hypoperfusion of the cardiopulmonary and veno-venous bypass, haemorrhage, and effect of nephrotoxic agents. Pulmonary embolism has also been demonstrated as a complication in early period post-CHLT [36]. Outcome results of patients receiving CHLT vary also due to different preoperative status of patients, with a number of patients especially in the early days presenting with a very poor clinical status at time of transplantation, contributing to the mortality rates.

It should be noted that any major cardiac surgery combined with liver transplantation is accompanied by an increased risk of severe fribrinolysis resulting in bleeding, and potentially hypotension and death. According to Parker et al, aprotinin administration throughout AVR-OLT procedure contributed also to prevention of fibrinolysis [17]. The same authors also hypothesized that increased donor organ ischemic time due to combined procedure of AVR-OLT could result in delayed function of allograft. Eckhoff et al reported development of several strategies to minimize complications in a patient undergoing a combination of AVR-CABG and OLT at the same time [47], by using a bioprosthetic valve, a saphenous vein graft and administration of aprotinin and conjugated estrogen.

Incidence of severe coronary artery disease in patients being evaluated for OLT reaches an impressive rate of 16.2%, with severe cardiac disease being a contraindication to liver transplantation. For reasons as the ones mentioned above, and for reasons that have been presented thoroughly previously, a combined cardiac procedure, including heart transplantation, CABG, and AVR, with liver transplantation appears to be a valuable option in certain cases.

A combined CABG-OLT would be indicated in the rare category of patients when percutaneous transluminal CABG is not amenable and cannot be performed prior to OLT, in patients with advanced but stable liver disease. These patients would otherwise be denied OLT. Similarly, a combined procedure of AVR and OLT could be a valuable option for patients with severe aortic stenosis and ESLD. On the other hand, indications for CHLT according to published data include end stage liver and cardiac disease, familial amyloidosis, hemochromatosis, familial hypercholesterolemia and homozygous b-thalassemia.

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