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Combined heart–liver transplantation: a single-center experience

Lucio Careddu,[1] Chiara Zanfi,[2] Antonio Pantaleo,[1] Anotonio Loforte,[1] Giorgio Ercolani,[2] Matteo Cescon,[2] Nicola Alvaro,[3] Emanuele Pilato,[1] Giuseppe Marinelli[1] and Antonio Daniele Pinna[2]

1 Cardiac Surgery Department, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy
2 Multiorgan Transplantation Department, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy
3 Regional Transplant Department, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy

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Correspondence
Dr. Lucio Careddu, Cardiac Surgery Department, S. Orsola-Malpighi Hospital, University of Bologna, Via Massarenti 9, 40138 Bologna, Italy.
Tel.: +390512143218;
fax: +390512143157;
e-mail: lucio.careddu@gmail.com

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Summary

Combined orthotopic heart and liver transplantation (CHLT) is a lifesaving procedure for patients with end-stage heart–liver disease. We reviewed the long-term outcome of patients who have undergone CHLT at the University of Bologna, Italy. Fifteen patients with heart and liver failure were placed on the transplant list between November 1999 and March 2012. The pretransplant cardiac diagnoses were familial amyloidosis in 14 patients and chronic heart failure due to chemotherapy with liver failure due to chronic hepatitis in one patient. CHLT was performed as a single combined procedure in 14 hemodynamically stable patients; there was no peri-operative mortality. The survival rates for the CHLT recipients were 93%, 93%, and 82% at 1 month and 1 and 5 years, respectively. Freedom from graft rejection was 100%, 90%, and 36% at 1, 5, and 10 years, respectively, for the heart graft and 100%, 91%, and 86% for the liver graft. The livers of eight recipients were transplanted as a "domino" with mean overall 1-year survival of 93%. Simultaneous heart and liver transplantation is feasible and was achieved in this extremely sick cohort of patients. By adopting the domino technique, we were able to enlarge the donor cohort and include high-risk patients.

Introduction

The first combined orthotopic heart and liver transplant (CHLT) was performed by Dr. Thomas Starzl in 1984 [1]. Nevertheless, it remains an uncommon procedure with very few reported cases [1–9].

Initially performed for patients with familial hypercholesterolemia, CHLT is currently performed for dual vital organ failure in amyloidosis, hemochromatosis, and familial hypercholesterolemia, as well as for patients with end-stage liver failure who are considered unfit for isolated liver transplantation because of severe heart disease [1,2,9–12].

Patients with liver failure and concomitant severe heart disease are candidates for CHLT, as the long-term survival after isolated liver transplantation is influenced only by the evolution of cardiomyopathy. The indications for CHLT should be expanded based on the improvements in operating techniques, immunosuppression, and length of survival in single-organ transplantation [5,6,8,13].

In the USA, the combined procedure is performed only at 15 heart and liver transplant centers. There is currently no consensus statement on CHLT, and long-term survival following the procedure remains unknown.

Here, we report a series of CHLTs performed at a single institution, highlighting a modification of the surgical procedure involving a standard heart transplant with the Yacoub technique and a piggyback technique without cardiopulmonary bypass for the liver transplant.

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Materials and methods

Patients

This study included 15 patients with heart and liver failure seen from November 1999 to March 2012 at the Cardiac Surgery and Multiorgan Transplantation Units of Bologna University. All patients were <65 years old when scheduled on the waiting list. The cause of the dual-organ failure was familial amyloid polyneuropathy (FAP) in 14 cases and chronic heart failure due to chemotherapy combined with liver failure due to chronic hepatitis with hepatitis C virus (HCV) infection in one patient [14]. The patients were 13 men (86.7%) and two women (13.3%) with a mean age of 50 (range 22–63) years. The inclusion criteria were based on patient status, the characteristics of the heart and liver disease, and a careful evaluation of the patients with FAP.

The pretransplantation evaluation included clinical and laboratory findings, echocardiography, left and right heart catheterization, routine chest radiography, carotid and peripheral arterial Doppler ultrasound, and total body computed tomography. The decision for combined transplantation was based on the consensus of the heart transplant team and multi-organ transplant team and involved cardiac surgeons, cardiologists, general surgeons, and hepatologists.

Thirteen of the patients underwent combined heart–liver transplantation, one underwent heart–liver–kidney transplantation, and one underwent only heart transplantation and was consequently excluded from this study.

The primary outcomes were patient survival and graft survival for both grafts. After transplantation, heart biopsies were performed routinely at 1 week and 1, 3, 6, and 12 months. Liver biopsies were performed when graft rejection was suspected based on serum hepatic enzyme levels.

In addition, the left ventricular ejection fraction, which was assessed by serial echocardiograms, coronary artery disease, cardiac index, central venous pressures, and pulmonary vascular resistance were determined by cardiac catheterization. Liver enzymes, bilirubin, liver ultrasonography, and biopsies were performed to assess liver function.

Relevant data collected included information on predictor variables, such as age, etiology, comorbidities, and severity of organ failure based on the model for end-stage liver disease (MELD) score and UNOS status (Table 1).

Immunosuppressive therapy

The immunosuppression induction protocol was based on thymoglobulin (1–1.5 mg/kg) for 3 days in 11 cases, and patient #11 and patient #5 did not receive it because of

Table 1. Population characteristics including principal recipient characteristics, domino liver transplantation, liver transplantation technique, and ischemia time of both organs.

Patient no	Sex	Age	MELD score reale	UNOS status	mPND score	Amiloidosis subtype	Domino liver transplantation	Liver transplantation technique	Heart ischemia time	Liver ischemia time
1	M	46.7	8	1B	Unknown	A-TTR Ser23Asg	No	Piggyback with by pass	Unavailable	Unavailable
2	M	16.1	6	1B	2	A-TTR Ser23Asg	No	Piggyback	3 h 10 min	5 h 20 min
3	M	38.2	7	1A	3	A-TTR Glu89Gln	No	Piggyback	2 h 30 min	7 h
4	F	63.5	7	1B	1	A-TTR Glu89Gln	Yes	Conventional technique	2 h 55 min	9 h 54 min
5	F	57.4	16	1A (ECMO)	0	N/A	No	Piggyback	2 h 59 min	7 h 25 min
6 (excluded from the study)	M	45.2	8	1B	1	A-TTR Glu89Gln	N/A	No liver due to hemodynamic instability	3 h	
7	M	63.1	10	1B	1	A-TTR Ser23Asg	Yes	Piggyback with by pass	3 h 10 min	9 h 5 min
8	F	45.3	7	1B	0	A-TTR Ser23Asg	Yes	Piggyback	1 h 54 min	6 h 50 min
9	M	59.1	32	1B	0	A-TTR Glu89Gln	Yes	Piggyback	2 h 33 min	7 h 40 min
10	M	38.9	9	1B	0	A-TTR Glu89Gln	No	Piggyback	3 h 20 min	7 h 15 min
11	M	39	8	1B	1	A-TTR Glu89Gln	Yes	Piggyback	2 h 40 min	8 h 5 min
12	M	53	7	1B	1	A-TTR Glu89Gln	No	Piggyback	2 h 42 min	6 h 30 min
13	M	63.5	6	2	1	A-TTR Glu89Gln	Yes	Piggyback	2 h 30 min	6 h 30 min
14	M	48.5	9	1B	1	A-TTR Glu89Gln	Yes	Piggyback	2 h 32 min	8 h 30 min
15	M	39	6	1B	1	mut TTR Ser 23 Asg	Yes	Piggyback	3 h 20 min	7 h

mPND, modified polyneuropathy disability.

leucopenia and HCV infection, respectively. At the beginning of this series, we did not use an induction therapy; therefore, patients #1, 2#, #3, and #5 did not receive it. The maintenance of immunosuppression therapy was based on steroids (1–2 mg/kg/day in two daily doses) and tacrolimus (blood level of 2–4 μg/ml) in three patients; mycophenolate mofetil (dose 1–2 g/day) was added in two patients. From 1999 to 2009, cyclosporine (7–10 mg/kg/day) was used instead of tacrolimus in 10 patients, and azathioprine was used in 4 of our first patients instead of mycophenolate mofetil.

Donor characteristics

All donors were matched by age, weight, height, blood group, and human leukocyte antigen type. They were 11 men and four women, mean age 31.3 ± 14.6 years. All donors had low inotropic support (low doses were defined as dopamine support <10 μg/kg/min, norepinephrine <0.05 μg/kg/min), except for one of them who received high doses of norepinephrine. The primary cause of death was head trauma. The grafts were procured during multiple organ recovery from the same donors. The heart and liver were flushed with Celsior solution and cold-preserved until 2008, when our institution switched to Custodiol cardioplegia (Custodiol HTK, Essential Pharmaceuticals, Newtown, PA, USA) for heart recovering. The ischemia times are summarized in Table 1.

Statistical analysis

The patients were stratified according to factors thought to influence survival: gender, cardiac comorbidity, preoperative symptoms, type of mutation, episodes of acute rejection, cold ischemia time, duration of surgery, intensive care unit stay, and total in-hospital stay after transplantation examining particularly in-hospital morbidity and mortality, overall rejection rate, domino transplant survival rate, and overall survival rate.

Survival was calculated using Kaplan–Meier curves. All statistical calculations were performed with SPSS 19 for Windows (SPSS, Chicago, IL, USA).

Operative technique

The hepatic and cardiac steps of the operation were performed by the respective surgical teams. The first step was transplantation of the donor heart into the recipient. The thorax was opened through a median sternotomy. Cardiopulmonary bypass was instituted with cannulation of both venae cavae and the ascending aorta. A standard cardiotomy was performed using the Yacoub technique. Typically, the pulmonary artery anastomosis was performed with the aortic clamp removed and the heart reperfusing. Once spontaneous cardiac function was satisfactory, the bypass was discontinued. After obtaining satisfactory hemostasis, the thorax was covered with a sterile drape leaving the gauze pads in the mediastinum. No drains were positioned during this phase of the operation to allow a better view of the operating field during the liver transplantation. A systolic blood pressure of 90–100 mmHg, diuresis of 10–20 ml/kg, and stable heart rhythm were mandatory for performing the subsequent liver transplantation. Then, the anticoagulation was reversed, and the liver was implanted. The abdomen was entered through a bisubcostal incision lengthened in the midline to the previous sternotomy. Orthotopic liver transplantation with preservation of the inferior vena cava (piggyback technique) was performed in all patients, except one who underwent caval anastomosis with the conventional technique. Before initiating the vascular reconstruction, perfect hemostasis of the surgical field must be achieved, and adequate vascular cuffs must be prepared. The liver allograft implantation begins with suturing the donor upper vena cava to the cuff created with the three recipient hepatic veins. Next, the portal or arterial anastomosis is performed, and the temporary portocaval shunt is taken down. After performing the cholecystectomy, the biliary tract is reconstructed with an end-to-end choledochostomy with a T-tube stent interposed. This orthostatic liver transplantation (OLT) technique can be performed with better hemodynamic stability, lower blood transfusion requirements, and shorter operating times than other reported in the literature. Two patients (#1 and #7) required venovenous bypass. In addition, patient #1 required a temporary portocaval shunt due to hemodynamic instability resulting from a decreased cardiac preload. OLT with liver splitting was performed in patient #12.

After all of the hepatic vascular and biliary anastomoses had been completed, the cardiac team returned to control any residual bleeding in the chest and to close it. All incisions were closed with standard techniques.

In domino OLT [15,16], the patient with FAP is donor and recipient simultaneously. It is necessary to achieve long arterial and portal segments for both the graft and patient. The common hepatic artery is clamped and divided just before the takeoff of the gastroduodenal artery. The portal vein is clamped and divided 1 cm below the portal bifurcation. Finally, the caval vein is divided above and below the liver [17]. In our series, the livers of eight recipients were removed with the inferior vena cava, flushed with cold Celsior solution, and transplanted as a "domino" in a new recipient. At our center, to decrease the time on a waiting list, the domino procedure was proposed for patients older than 60 years with hepatitis C or B complicated by malignancy.

Results

The main perioperative data for the 15 patients are summarized in Table 1. Two deaths occurred during the follow-up period, which ranged from 1 to 13 years.

One in-hospital death (patient 2) occurred 60 days after CHLT. The patient underwent two sternotomies for bleeding. First, the heart transplant team revised the caval anastomosis on postoperative day (POD) 1; then, he was re-operated on for intrapericardial bleeding on day 7. Continuous venovenous hemodialysis was required for renal failure from day 8. A cardiac biopsy performed on day 20 showed type 1B rejection, which was successfully reversed with thymoglobulin. One month after CHLT, the liver transplant team performed a relaparotomy for hemoperitoneum, without detecting the bleeding source. The patient developed sepsis and died from multi-organ failure on POD 60.

Patient #3 developed intestinal ischemia at the end of the CHLT, and a right colectomy and ileostomy was required. The histology showed submucosal hemorrhage, with massive perivascular, muscular, and perivisceral amyloid deposition. The postoperative course was characterized by orthostatic hypotension and dehydration due to vomiting and massive fluid loss through the stoma, which resolved after stoma closure performed 3 months later. Subsequently, bowel dysmotility with episodes of vomiting persisted, and rehospitalization was required 10 months after CHLT to treat moderate renal dysfunction caused by rapid dehydration. Despite a good recovery of cardiac and hepatic functions, the other systemic symptoms of FAP did not improve during the follow-up and he died at home from an unknown cause 20 months after CHLT.

After transplantation, heart biopsies were performed routinely at 1 week and 1, 3, 6, and 12 months. Liver biopsies were performed when graft rejection was suspected based on the serum hepatic enzyme levels.

Two episodes of grade III heart rejection occurred in patient #8: one episode at 6 months and another persistent episode due to grade III rejection 5 years after transplantation. The first episode was treated with three 1-g boluses of steroids. The other episodes were treated with the same dose and plasmapheresis.

Grade I liver rejection occurred 1 month after transplantation in patients #4 and #10, and both were treated with two 1-g boluses of steroids.

The survival at 1 month and 1 and 5 years was 93%, 93%, and 82%, respectively (Fig. 1). The freedom from graft rejection at 1 month and 1, 5, and 10 years was 100%, 100%, 90%, and 36%, respectively, for the heart graft and 100%, 100%, 86%, and 86% for the liver graft.

All the remaining patients with amyloidotic disease did not show any sign of progression of neuropathic disorders or sign of gastrointestinal or ocular disease during the follow-up.

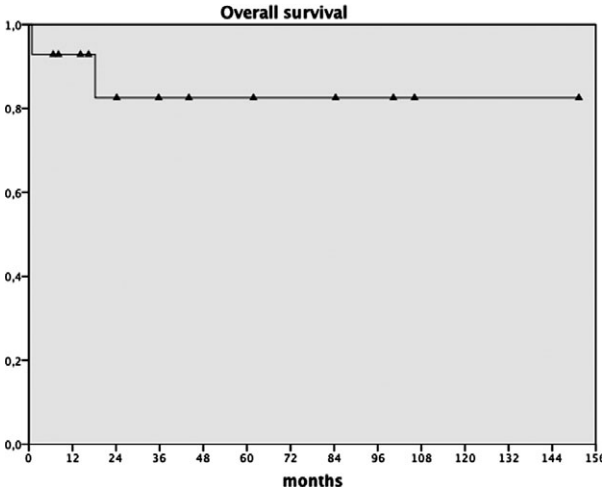

Figure 1 Overall survival.

We performed liver biopsies in five domino liver recipients. No signs of rejection or amyloid disease were observed.

The mean overall survival for the patients with a domino liver was 93% at 1 year; recurrence of chronic C hepatitis was the major complication of the transplanted domino grafts.

Discussion

Starzl [1,2] reported the first successful CHLT in a 6-year-old girl with familial hypercholesterolemia in 1984. In the last 10 years, the surgical procedure for CHLT has evolved tremendously and has improved owing to recent advances in surgery and in the adoption of more effective immunosuppressive agents. The most recent United Network for Organ Sharing (UNOS) data indicate the 1- and 3-year survival rates to be 84.8% and 79.5%, respectively, comparable to the rates for single-organ transplantation (liver or heart alone) [5]. Only a few transplant centers are capable of performing this delicate procedure. Consequently, a limited number of recipients have been treated successfully and described. Our single-center experience is comparable to previously reported series [5,8,9]. The longest survival in our population has been 12 years, confirming the long-term benefits of CHLT in well-selected patients.

Our most common indication for transplantation was amyloidosis. The recipients were younger than those reported elsewhere. They were mainly male, similar to reports on single-organ liver or heart transplantation [7,8,12].

Amyloidosis is a familial metabolic disorder in which insoluble amyloid protein is deposited in the kidneys, nervous system, heart, and liver. In 14 cases in our series, the amyloidosis was characterized by an autosomal-dominant disorder, which led to the deposition of a mutant transthyretin (TTR) mainly produced in the liver. The literature reports that liver transplants were the first established treatment for familial amyloidosis with TTR mutations. However, cardiac TTR variants have recently been shown to involve cardiac tissue slowly, silently leading to progressive myocardial dysfunction. Moreover, the absence of neurological symptoms may delay patients from seeking medical attention. Consequently, CHLT needs to be considered early despite the absence of clinically relevant cardiac involvement at the time of liver transplantation because myocardial infiltration in TTR seems to require a longer time to develop neurological and constitutional symptoms. [18].

Combined heart–liver transplantation can also be considered in cases of genetic hemochromatosis and familiar hypercholesterolemia, although we did not have any such cases [1,2,10,11].

Once a candidate has been listed for CHLT, allocation of the two organs is dictated by the listing priority of the organ with the highest life-threatening risk. Mostly, the priority is driven by symptomatic cardiac dysfunction, even if a hepatic disorder might sometimes allow the heart to be allocated along with the liver graft.

The waiting time for transplantation is another parameter that plays an important role in early referral. Most of our patients deteriorated dramatically during the wait, with progression to autonomic involvement of the disease. Porrett *et al.* [19] reported the mortality rates on the waiting list for CHLT candidates and found that patients with MELD scores of 20–29, and cardiac status two had poor results. Consequently, at our institution, CHLT is considered early in patients with cardiac status 1A/1B or patients with MELD scores <30, particularly in the case of a confirmed diagnosis of amyloidosis [13,19].

In addition, in our experience, poor nutrition, a high polyneuropathy disability score, and long disease duration should be evaluated before the CHLT procedure (Table 1).

Surgically, we proceed first with a standard heart graft implantation, as described above. Then, the systemic intravenous heparin infusion is neutralized fully, and the patients' hemodynamics are evaluated. In the case of primary heart graft failure or no satisfactory postimplantation clinical stabilization, even with the use of inotropes or mechanical circulatory support, liver transplantation is no longer considered, as in one case in our population. Therefore, CHLT requires a successful heart graft implantation.

After OLT, some complications of venovenous bypass have been described, and some hemodynamic changes cannot be avoided. In 1989, Tzakis *et al.* [20] described the preservation of the inferior vena cava during OLT. This procedure, called the "piggyback" technique, improves hemodynamic stability during the anhepatic phase. Moreover, cirrhotic patients could better tolerate the portal clamping without the need for anticoagulation during OLT performed using venovenous bypass.

Currently, 12 of the 14 patients who underwent CHLT in the present study are alive. We had one in-hospital death and a second patient died 20 months after the CHLT from unknown causes. Both patients were in poor clinical condition pre-operatively, as reflected by prolonged malnutrition and evident weight loss (cachexia). In patients in good preoperative condition, the mortality and long-term survival after CHLT for FAP might be better than for isolated heart and liver transplantation procedures.

Single OLT recipients can tolerate lower levels of immunosuppression with a relatively lower risk of graft rejection compared to heart or kidney transplant recipients. A similar beneficial effect has been reported for combined liver–kidney transplantation, although the mechanism of this unexplained protective effect of the liver graft remains unclear [21,22]. Lower acute rejection rates have been reported in clinical CHLT when compared to single-organ recipients, and it might be due to a better "tolerance" of heart grafts in the setting of a concomitant liver graft. In our CHLT recipients, we were able to maintain good graft function with a low immunosuppression regimen, reducing the immunosuppressive therapy to a single immunosuppressive agent plus steroids in 30% of the recipients. Despite the lower immunosuppression, the rates of liver and heart grafts without rejection were 90% and 86%, respectively, at 5 years, and 36% and 86% at 10 years. Most of the liver rejection occurred during the first post-transplant year.

To overcome the lack of donor livers, many surgical techniques have been developed. Domino liver transplantation was described in the mid-1990s [15]; it consists of using liver grafts procured from other organ transplant recipients scheduled for CHLT. Liver failure has never been reported in the amyloidotic disease scenario. Because amyloidosis generally has an onset in the third decade of life and carriers of the trait might never develop the disease, sequential liver transplantation using amyloidotic livers can be performed as a "domino" procedure. No amyloid disease has been reported in recipients after the procedure [15,16]. At our center, to decrease the time on the waiting list, the domino procedure was proposed to patients older than 60 years with hepatitis C or B complicated by malignancy; one case was performed in a 33-year-old woman who had previously undergone a liver living-donor procedure for cholangiocarcinoma and was retransplanted with an amyloidotic liver due to hepatic artery thrombosis. We

performed eight domino transplants in the CHLT in 14 recipients. Despite the marginal recipients, the domino liver procedure resulted in a 1-year survival of 93%.

In conclusion, our series confirms that combined heart–liver transplantation is a safe, feasible treatment for selected patients with heart and liver disease who otherwise would be disqualified from receiving either a heart or a liver graft alone. The clinical outcomes of this combined procedure are comparable to those of heart- or liver-only transplantation, with favorable outcomes, and low peri-operative mortality. This complex procedure should be performed in select, high-volume transplant centers. An accurate pre-transplantation recipient evaluation is necessary for optimal organ allocation. Based on our experience and a wealth of reports [3–9], we believe that combined heart and liver transplantation is a therapeutic option for patients with combined heart and liver failure and the availability of this lifesaving procedure needs to be promoted in both the medical community and general public.

Authorship

LC and CZ: elaborated and collected the data and wrote the manuscript. The Authors contributed equally to the crafting the following manuscript. AP, AL, GE and MC: collected the data and reviewed the manuscript. NA: collected the data. GM: reviewed the manuscript and provided support as senior reviewer. AP: collected the data, reviewed the manuscript and offered support as senior reviewer.

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