ORIGINAL ARTICLE

Combined Transplantation: Survival and Complications in Heart-Lung and Heart-Kidney Transplant. A single institution experience

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Objective. **Multi-organ transplants (MOT) have been increasing. The most common are Heart-Kidney (HKT) and Heart-Lung (HLT). We present our experience, morbidity and mortality on HKTand HLT. *Material.* This is a retrospective review of all HKT and HLT between January 2015 and May 2022. Patient transplants were performed at a single large referral center. Patient demographics, morbidity and mortality were collected. *Results.* Seventeen HLT and 8 HKT were performed. On the HLT, mean age was 37 ± 15.6 years. The most common indication for ECMO support was acute cor pulmonale (73%,). The most common complications on ECMO support were bacteremia 82%. Post-transplant complications included vocal cord paralysis on 36% .The mortality in the ECMO B-HLT group was 9% at thirty-days and 18% at one year mortality . Follow-up was at 7 years. Long term mortality was 15 %, 30 % with at least one acute episode of rejection, 15% had evidence of Bronchiolitis Obliterans Syndrome (BOS). On the HKT, the mean age was 51.2 ± 10.7. The most common diagnosis was Idiopathic Cardiomyopathy (50%) and hypertensive nephropathy. All HKT was performed in 2 stages, Mortality was 12% (n=1) during the first year, and 12% later. Complications were 12% with severe primary graft dysfunction of the heart, 25% developed coronary artery vasculopathy (CAV). The most common complication was infection (62 %). *Conclusions.* Outcomes of HKT and HLT are highly favorable, preferred treatment option for select patients. In appropriately selected patients, can be undertaken with acceptable morbidity and conditional survival.**

Key words: Complications; ECMO as a bridge to transplant. Heart-Kidney transplant; Heart-Lung transplant; Survival.

Objetivo. **El transplante de múltiples órganos se ha incrementado progresivamente. Los más comunes son corazón-riñón (HKT) y corazón-pulmón (HLT). Presentamos nuestra experiencia, morbilidad y mortalidad en HKT y HLT. *Material.* Este es un estudio retrospectivo de un centro de referencia , incluye todos los casos de HLT y HLK entre enero 2015 y mayo 2022. Las variables demográficas, uso de ECMO, mortalidad y morbilidad fueron analizadas. *Resultados.* Diecisiete pacientes de HLT y 8 HKT fueron incluudos. En HLT, la edad promedio fue 37 ± 15.6 años. La indicacion más común para ECMO fue cor pulmonale agudo (73%). La complicación más común durante ECMO fue bacteremia 82%. Las complicaciones post-transplante incluyeron parálisis de cuerdas vocales en 36%. La mortalidad en el grupo ECMO B-HLT fue 9% a 30 dias y 18% a un año. El seguimiento fue de 7 años. La mortalidad a largo plazo fue de 15%. Treinta por ciento tuvieron al menos un episodio de rechazo, y 15% evidencia de Bronquiolitis Obliterante. En los casos de HKT, la edad promedio fue 51.2 ± 10.7. El diagnóstico más común fue cardiomiopatía idiopática (50%) y nefropatía hipertensiva. El HKT se realizó en dos fases (primero corazón, y horas después, riñón) . La mortalitdad fue 12% en el primer año, y 12% después. Las Complicaciones fueron 12% para disfunción primaria del aloinjerto cardiaco, y 25% para enfermedad coronaria (CAV). La complicación más común fue la infección (62 %). *Conclusiones.* Los resultados de HKT y HLT son una opción de tratamiento altamente favorable y preferida para pacientes seleccionados, con morbilidad y supervivencia condicional aceptable.**

Palabras clave: **Complicaciones; ECMO como puente al trasplante; Trasplante corazón-riñón; Trasplante corazón-pulmón; Sobrevida**

Cir Card Mex 2023; 8(1): 5-11.

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The frequency of multi-organ transplants (MOT) has risen considerably over the past two decades, and up to 90% include a kidney [1,2] Due to organ scarci-

ty, increased MOT utilization may disadvantage candidates with end-stage kidney disease (ESKD) awaiting kidney-alone transplantation (KAT) [3,4]. While liver, heart, and lung allocation systems utilize medical urgency and disease severity to determine allocation priority, the kidney allocation system (KAS), implemented in 2014, utilizes qualified wait-time to determine allocation sequence, and prioritizes highly sensitized candidates, prior living donors, human leukocyte antigen (HLA) zero-mismatch pairs, and pediatric candidates. Heart transplantation (HT) is the therapy of choice for select patients with end-stage heart disease. Patients with severe heart disease frequently have concomitant kidney disease. These patients with kidney disease who undergo heart transplant alone have reduced survival. Kidney failure is a predictor of morbidity and mortality in post–heart transplant patients [5,6]. Simultaneous heart-kidney transplant (HKT) has enabled the successful transplantation of patients with end-stage heart disease and concomitant kidney disease, with increasing numbers since 2010. Kidney injury is a known and relatively common sequalae of end stage heart failure, and ESKD can occur in the setting of heart transplant [6]. Dialysis after heart transplant adds to complexity of care, cost, and morbidity [7,8]. HKT can mitigate the effects of suboptimal kidney function during the perioperative period, and several retrospective studies have demonstrated improved survival after HKT compared with HT alone among patients on dialysis or with reduced GFR [6,9] Perhaps in response to the emerging recognition of these benefits, HTK has experienced the largest increase in frequency of all MOT in the past 5 years [10]. This rise in HKT has been facilitated by the current allocation system, in which all HKT candidates are prioritized above all candidates waiting for a kidney transplant alone (KT), with no standard criteria for HKT eligibility [11]. In contrast, those with persistent kidney dysfunction after HT-only receive no such priority and, in the absence of a living donor, face the same expected wait time for a deceased donor kidney (DDK) as KT-only candidates [12,13]. Such a policy produces an obvious incentive to favor HKT over HT-only whenever the reversibility of an HT candidate's kidney dysfunction is in question.

In the early1990s, multiorgan transplant procedures that included transplantation were almost exclusively HKT. Although heart-lung transplantation (HLT) remains the most common of the multiorgan lung transplants, other procedures, in particular lung-liver and lung-kidney transplantation, have become relatively more common, particularly in the last decade [14]. Combined HLT is an accepted treatment modality for selected patients with end-stage cardiac and pulmonary failure. Historically etiologies leading to HLT are congenital heart disease, idiopathic pulmonary arterial hypertension, cystic fibrosis, and refractory right heart failure in the setting of chronic lung disease.

According to the Organ Procurement and Transplantation Network (OPTN), the number of combined HLT performed in the United States has drastically increased in recent years. During 2011, 27 HLT were performed in the US reaching a nadir of 15 HLT in 2015, subsequently rising to 58 and 45 HLTs in 2020 and 2021 respectively [14]. The cause for the increase in the use of HLT is likely multifactorial and it may reflect the impact of recent changes in organ allocation policy in thoracic transplantation in the US. The United Network for Organ Sharing (UNOS) revised its thoracic organ allocation policy with the goal of reducing the wait list mortality for both lung (2006) and heart transplantation (2018) [15,16]. As a result of policy changes there has been an increase in utilization of ECMO as a bridge to lung transplantation, and more recently, as a bridge to heart transplantation. Several studies have shown that waitlist mortality has substantially decreased with minimal decline in post-transplant survival [17-19].

MATERIAL

We retrospectively reviewed all patients undergoing combined HLT and combined HKT at the University of Alabama at Birmingham (UAB) from January 2015 to May 2022.

Patient characteristics included, baseline demographics, age, sex, primary diagnosis, use of ECMO, complications while on ECMO support, intra-operative data included total ischemic time, warm ischemic time, cardiopulmonary bypass time, and cross-clamp time were recorded. Post-transplant

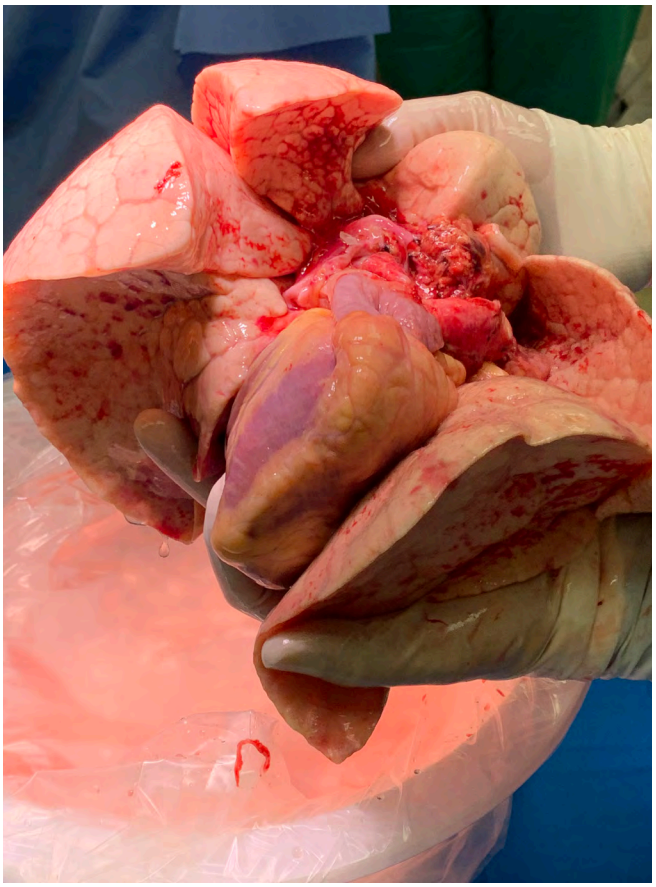

Figure 1. Heart-lung block

Table 1. Preoperatives Variables on Patients ECMO BT-HLT

VARIABLE	ECMO BT- HLT (n=11)
Age	**37 ± 15.57**
Gender (Female)	5 (45%)
Indication	
Cystic fibrosis/ Congestive Heart Failure	**01**
Acute cor pulmonale /Secondary Pulmonary Hypertension and Interstitial Lung Disease	05
Acute Cor Pulmonale / Primary Pulmonary Hypertension and No Ischemic cardiomyopathy	01
Acute cor pulmonale ,/Primary Pulmonary Hypertension	01
Acute Cor Pulmonale /Secondary Pulmonary Hypertension and COPD / Ischemic cardiomyopathy	**01**
End-stage lung disease, Necrotiziting pneumonia / Congestive Heart Failure	01
Sarcoidosis	**01**

BT-HLT: Bridge to Heart-Lung Transplant

outcomes recorded included postoperative complications, and post-transplant mortality. The details for procurement and implant technique of the Heart/Lung block have been described in detail in a previous article [20] (**Fig. 1**).

Table 2. Postoperative Complications on Patients ECMO B-HLT

CASE	COMPLICATIONS
1	AKI, Sepsis, heart/lung graft failure.
2	AKI, left vocal cord paralysis s/p left vocal cord medialization; sternal dehiscence.
3	AKI requiring CRRT/ iHD; CMV viremia; positive DSA received Thymoglobulin; gastroparesis and severe esophageal dysmotility with PEG tube placement; sepsis due to PEG tube dislodgement requiring emergent ex-lap.
4	Klebsiella bacteremia/pneumonia.
5	Chylorthorax; AKI requiring CRRT; IVC thrombus with mechanical thrombectomy; tracheal anastomosis requiring stent placement, DSAs + s/p IVIG infusions; SMA bleed - Embolization in IR , Exploratory lap with 2.5L blood removed. Ascites Fluid + Enterococcus. Thoracotomy for Tracheal reconstruction with muscle flap over tracheal dehiscence; pt placed on fem-fem VA ECMO during procedure for hemodynamic instability. Complicated with right hemothorax with thoracotomy. Redo sternotomy aortic repair, tracheal dehiscence reconstruction with pericardial tissue flap and open sternum wound vacuum assisted closure Post op course complicated with bleeding , mediastinal exploration in OR. Developed SAH and MOF.
6	Esophogeal rupture post-transplant, stent placed, L sided empyema, AKI, deconditioning, vocal cord paralysis (s/p medialization), R fem Artery thrombus (s/p embolectomy, myoplasty), and idiopathic inflammatory plexopathy; Bacteremia: Streptococcus mitis/oralis, Enterococcus faecium; T2: Positive for Candida. Readmitted for respiratory failure,required VV EMCO, PNA, sepsis, leucopenia, AKI, CRRT, MOF.
7	Aortic injury (descending) during the transplant, with exsanguination on VA ECMO in the first 24 hours.
8	Vocal cord paralysis , AKI.
9	VV ECMO post op for PGD.
10	Tracheal dehiscence, COVID, Thoracotomy with Tracheal reconstruction with pericardial patch and muscle flap. Chest wall hematoma drainage, gastroparesis with GJ tube placement.
11	Gastroparesis with GJ tube, muscle flap in right groin for infection post decannulation.

AKI: Acute kidney injury, CRRT: Continuous renal replacement therapy, iHD: intermitent hemodialysis, CMV: Cytomegalovirus, DSA: Donor specific antibodies, PEG: Percutaneous endoscopic gastrostomy, IVC: Inferior vena cava, IVIG: Intravenous inmunoglobuline, SMA: Superior mesenteric artery, IR: Interventional radilogy, SAH: subarachnoid hemorrage, MOF: Multiorgan failure, PNA: Pneumonia, PGD: Primary graft dysfunction.

RESULTS

From 2015 to 2021, 25 patients have undergone combined thoracic transplantation. 17 heart-lung and 8 heart-kidney at our institution. Since 1998, fifty patients have received a heart - lung block. In this study, since 2015, 11(64%) patients required ECMO support prior to transplantation (ECMO BT-HLT). The mean age was 37 ± 15.6 years. The group was almost equally distributed by gender with nine females (54%) and eight males (46%). The mean BMI was 23 ± 6.4. Blood group A was found in 6 patients) (54 %) of the group.

For the 11 patients with ECMO BT-HLT, the median duration of ECMO support prior to transplantation was 41 ± 34.7 days. The most frequent indication for emergent VA ECMO support was acute cardiogenic shock associated with acute cor pulmonale (**Table 1**). All patients were listed as historical UNOS heart status 1A or, after 2018, status 1 of the current UNOS urgency status. All the patients had a peripheral cannulation strategy, just 18% (n=2) were an open cannulation. The mean lung allocation score was 78 ± 18.3. The median waitlist time was 8 days.

Complications while on ECMO support were common. Bacteremia 82% (9 patients) and AKI on 54% (6 patients), and 18% required continuous renal replacement therapy (n=2). One patient required reoperation for axillary graft bleeding and ECMO reconfiguration, one patient developed pancytopenia, one pediatric patient needed circuit change for air in circuit and thrombosis and sternotomy with pericardial clot evacuation. All patients were ambulatory and infection free at the time of transplant.

Regarding operative variables, the mean allograft ischemic time was 226 ± 45.8 minutes, the mean warm ischemic time 52.9 ± 17.5 minutes, the mean cardiopulmonary bypass time 447 ± 84, and the mean aortic cross-clamp time was 150 ± 32.0 minutes.

The granularity of the postoperative complications is high (**Table 2**). Post-transplant complications included vocal cord paralysis in 4 patients (36%), thromboembolic events 36% (n=4), 3 patients (27%) developed early primary lung graft dysfunction and required post-transplantation ECMO support, 3 patients (27%) developed post-operative pneumonia, 3 patients (27%) requiring continuous renal replacement therapy and another 3 patients (27%) required a surgical enteral access (gastrostomy or gastrojejunostomy)

Table 3. Late Complications on HLB Patients

LATE COMPLICATIONS	HLB PATIENTS (n=15)
Acute Rejection	4 (30%)
Diabetes	3 (23%)
Severe Renal Dysfunction (no dialysis)	2 (15%)

HLB: Heart-Lung Block

Table 4. Primary Cardiac Disease on HK Patients.

DIAGNOSIS	HK Patients (n=8)
Idiopathic Dilated Cardiomyopathy	4 (50%)
Ischemic Cardiomyopathy	2 (25%)
Dilated Cardiomyopathy: Adriamycin	1 (12.5%)
Dilated Cardiomyopathy: Post partum	1 (12.5%)

HK: Heart-Kidney

to ensure enteral nutrition, Surgical complications included 2 patients(18%) with tracheal dehiscence and 1 patient (9%) who developed an intraoperative aortic dissection. The length of ICU stay post-transplant was 20.5 ± 22.6 days and length of stay from the transplant to discharge was 65 ± 80.2 days. Patients who received ECMO as BT-HLT at UAB had a 1-month post-transplant mortality of 9%.During 7 years of follow up (**Table 3**). Long term mortality for all the survivors with HLT is 15 % (n=2) there has been 4 patients (30 %) with at least one acute episode of rejection, 3 patients (23%) had a new onset of diabetes and 2 patients (15%) experience severe renal dysfunction (no dialysis). All the survivors have the grafts functioning, no evidence of coronary artery vasculopathy (CAV). However, 15% (n=2) had evidence of Bronchiolitis Obliterans Syndrome (BOS). There has not been any stroke, infection or malignancy.

Since 1995, thirty-nine patients have received a heart-kidney transplant (HKT). In this study, since 2015, 8 patients underwent to this combined transplant. The mean age was 51.2 ± 10.7, 25% (n=2) were female. Blood group O was found in four patients (50 %) of the group. The most common diagnosis for the heart transplant side was Idiopathic Cardiomyopathy on 4 patients (50%). At the other hand, the most common indication for the kidney transplant was end stage renal disease secondary to hypertensive nephropathy (**Table 4**). The measured creatinine clearance at transplant was 42.6 ml/min (± 19.9), the serum Creatinine at time of surgery was 2.8 mg/ml (± 1.8). Regarding operative variables, the mean allograft ischemic time was 265 minutes, the mean warm ischemic time on the heart was 55.9 ± 11.5 minutes, the mean cardiopulmonary bypass time 164± 80, and the mean aortic cross-clamp time was 134 ± 92.0 minutes. All our HKT are performed on 2 stages, starting with the heart, the time between the heart transplant and the kidney transplant was 567 min (± 437.5). Mortality was 12% (n=1) during the first year, and another 12% (n=1) during the next 6 years. Complications directly related with the grafts included 1 patient (12%) with severe Primary graft dysfunction of the heart, and 1 patient required dialysis in the first 48 postoperative, he recovered the renal function, but eventually had irreversible renal graft failure 3 years later (**Table 5**). Of note, creatinine at discharge in the six patients without postoperative renal failure was 1.3 mg/ml (± 0.5). During the follow-up, two patients (25%) developed coronary artery vasculopathy (CAV).

Table 5. Late Complications on HK Patients

LATE COMPLICATIONS	HK Patients (n=7)
Diabetes	4 (50%)
Infection : Bacterial	3 (37%)
Infection: Fungal	2 (25%)
Infection: Viral	2 (25%)
Cancer : Skin	2 (25%)
Cancer: Lung	1 (12.5%)
CAV	2 (25%)
Primary Graft Dysfunction: Heart	1 (12.5%)
Dialysis	1 (12.5%)
Stroke	1 (12.5%)

CAV: Coronary artery vasculopathy.

Post-transplant complications of the HKT patients no related directly with the grafts were stroke in one patient, (12%), 3 patients (n=37%) had cancer after surgery. The most common complication was the infection, (62 %) (n=5), diabetes of new onset after the transplant was developed in 4 patients (50%), and there was a total of 10 rejection events during this 7-year period of follow-up.

DISCUSSION

The first implantation of a heart-lung block was performed by Dr. Denton Cooley in 1968. The operation was performed on a two-year old patient who unfortunately succumbed 24 hours post-transplant. Over the following decade pioneering research by the Stanford University group led to the first successful combined heart and lung transplant. The operation was performed by Dr Bruce Reitz and Dr Norman Shumway in March 1981. Mary Golkhe, a 45-year-old with primary pulmonary hypertension was the recipient. Mrs. Golkhe survived for 5 years and there was no evidence of rejection at the time of her death [21].

Most patients undergoing HLT in recent years have done so for various forms of pulmonary hypertension. Before 2018, the volume of HLT were declining over the years, but recently, the number of combined HLT performed in the United States has drastically increased in recent years, reaching a nadir in 2020 with 58 procedures. This could be a result of the recent changes in organ allocation policy in thoracic transplantation in the US. The 35th annual report of the ISHLT registry reported on 3,998 patients undergoing combined heart and lung transplantation between 1992-2016. The early survival following heart-lung transplantation is worse than lung transplantation, with a median survival of 3.3 years for those transplanted in 1982 to 2015 [22].

In recent years, overall mortality after HLT has decreased, this can be attributed to improved surgical techniques, better organ preservation solutions, and the use of tacrolimus for immunosuppression. (23). The reported survival was 81.3% at 1 month, 66.4% at 1 year, 47% at 5 years, and 35.6% at 10 years. Median survival was 4.6 years and median conditional

survival was 11.2 years for patients that survived one year after HLT. Perhaps, a more valid measure is conditional median survival, which is defined as median survival for all patients who survive to 1 year. There has been a statistically significant improvement in survival for the cohort of patients transplanted since 2004 compared to prior cohorts. The group transplanted after 2004, like our patients, achieved a median survival was 5.4 years and median conditional survival was 11.5 years [24]. The conditional survival of our cohort is excellent, with just 15% of mortality at 7 years. Currently, most of the heart-lung transplants are performed on patients with severe pulmonary hypertension associated to congenital heart disease, although there is a recent trend towards more HLT for interstitial lung disease [14,24].

In our ECMO patients, 5 of the 8 patients with cardiogenic shock secondary to acute cor pulmonale had history of interstitial lung disease. Our patients with cystic fibrosis and congenital heart disease did not need ECMO support. Although the experience with ECMO as a BTLT is encouraging, there is limited evidence to use ECMO as a bridge to HLT. A previous analysis by Sertic et al, reported 1039 adult HLT in the UNOS database between 1987 and 2018. Mortality at 30-day for the ECMO, and no support groups was 50% and 16% respectively ($p<0.0001$). Mortality at 1-year mortality for the same groups was 50% and 31%, ($p<0.0001$). The use of ECMO as a bridge to transplant were identified as strong predictors for in-hospital mortality [25]. In a contemporary study utilizing the United Network of Organ Sharing (UNOS) database HLT patients, pretransplant ECMO was also shown to be a significant predictor of death or retransplantation [26]. In contrast to registry data, reports from institutions with substantial experience in heart and lung transplantation have not encountered a detrimental effect to ECMO use prior to transplantation. The Stanford University group reviewed all HLTs performed between 2013 and 2020. eight patients received ECMO pretransplant. Pretransplant ECMO did not increase the operative time, the necessity postoperative mechanical circulatory support or intensive care unit stay. In the ECMO cohort, the 30-day, 1-year, and overall survival after transplantation were 87.5%, 87.5%, and 75.0%, respectively. There was no significant difference in survival for the BT HLT group and the overall group [27].

Our results confirm the findings of the Stanford University group. While overall mortality after HLT has decreased, morbidity has remained relatively constant, generally due to malignancies, infections, and chronic allograft dysfunction, and more recently, the morbidity associated with ECMO is important. In our institution we have a protocol for femoral ECMO ambulation [28]. Multiple studies by other authors have reported the feasibility and safety of ambulating patients with femoral cannulas [29,30]. We believe ambulation is crucial to prevent complications, deconditioning, and diaphragmatic weakening, and reduces hospital length of stay. Several studies have demonstrated that physical rehabilitation in patients on ECMO support is safe and can potentially improve post-transplant recovery and outcomes [31,32]. The morbidity due to chronic cardiac allograft dysfunction is significantly lower among HLT patients compared with those with isolated heart transplant. This phenomenon is known as the "combi-effect" [33]. The bronchial lymphoid tissue in the lung may localize the host immune response, thereby protecting the cardiac allograft from immune-mediated injury. Although this apparent cardiac allograft protection in HLT, the lung allograft does not derive this same benefit [34]. However, ISHLT data suggest that rates of obstructive chronic lung allograft dysfunction are lower in HLT patients compared with LT recipients at 1- and 5-years post-transplant (7.1%) and 31% VS 9.3% and 41%). Our incidence of BOS at 7 years is 15%, and all the survivors have the grafts functioning without no evidence of CAV.

Although chronic allograft dysfunction and infections are responsible for most long-term complications and mortality after HTL, malignancies also occur commonly. In our cohort, there has not been any major infection or malignancy during the follow up. Tracheal dehiscence is a dreaded and challenging surgical complication. We have 2 cases of late anastomosis dehiscence, the first one was a late dehiscence (almost one month after the HLT) in a pediatric patient, reoperation with tracheal re-anastomosis was successful, unfortunately the patient died weeks later from multiorgan failure. The second case was a patient infected with COVID-19 in the postoperative period; the patient underwent early surgical reconstruction with bovine pericardial patch and a reinforcement with a muscle flap and had a successful recovery (**Fig. 2**) (**Fig. 3**).

HKT was first described in 1978 by Norman et al. [35]. End-stage heart failure patients often present with severe kidney failure and have limited treatment options. The approach of this entity is still controversial and complex. Now, HKT is a recognized therapy for simultaneous end-stage cardiac and

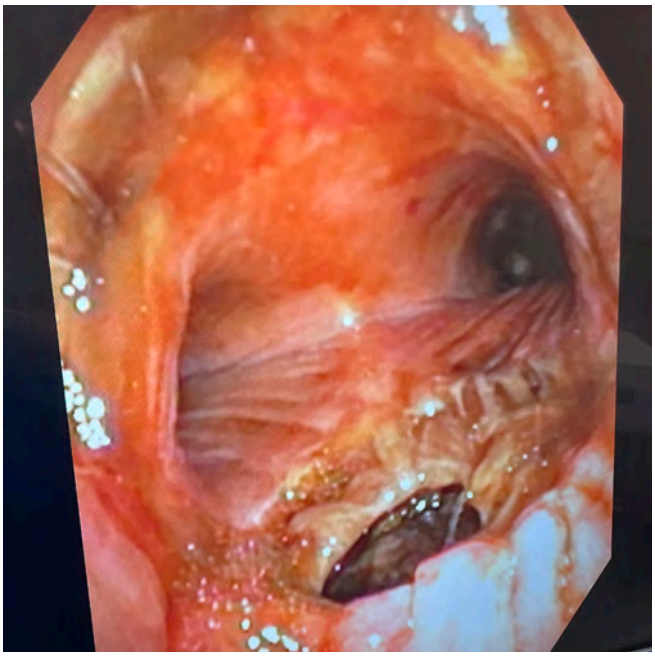

Figure 2. Postoperative tracheal dehiscence.

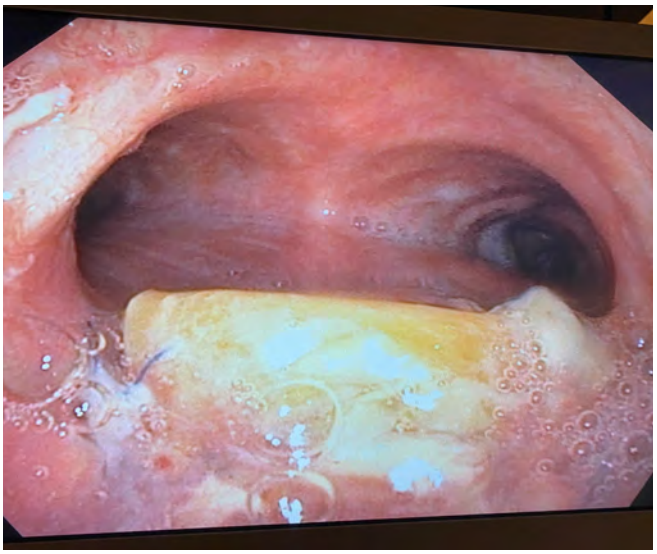

Figure 3. Follow up bronchoscopy with completed sealed of the defect and no leak was observed.

renal dysfunction. However, the ability to predict renal recovery in patients with heart failure is limited. Many of these patients with renal insufficiency have cardiorenal syndrome, and HT alone may lead to renal recovery. In these patients, a staged approach may be the most judicious use of scarce organs. In some patients, the KT at the time of the HT may actually lead to worse kidney graft survival given the delicate hemodynamic values and vasopressor requirement in the perioperative period [36]. Indication for HKT is supported by UNOS registry analysis, which shows increased mortality associated with lower pre-HT estimated glomerular filtration rate (eGFR), and improved posttransplant survival with HKT versus HT in patients with eGFR < 37 mL/min/1.73m2.

According with the consensus of the American Society of Transplantation (AST) on 2019 [37] the recommendations for HKT vs KT are: Patients with CKD and patients with AKI that persists despite optimizing cardiac function for a period to allow for kidney recovery are viewed as having kidney disease that is established and not reversible.

a. Patients with established GFR < 30 ml/min/1.73 m2 may be considered for HKT.

b. Patients with established GFR of 30–44 ml/min/1.73 m2 and firm evidence of CKD in the presence of stable hemodynamics may also qualify for HKT on an individual basis.

c. Patients with established GFR of 45–59 ml/min/1.73 m2 may not be appropriate for HKT.

This has resulted in an exceptional rise in HKT in US, with a nearly 5-fold increase from 2011 to 2021. At the same time, however, UNOS data comparing HKT to KT after HT shows some contradictory results, with significant survival disadvantage for simultaneous multiorgan transplant as opposed to sequential [38]. On the other hand, Agarwal et al. found comparable long-term survival between all HKT and HT patients in UNOS up to 2019 (median 12.4 vs 11.3 years, P = .053), with significant survival benefit in patients with eGFR < 45 mL/min/1.73 m2 (median 13 vs 10.2 years; p < 0.001), and patients on pre-transplant dialysis (median 12.4 vs 9.9 years; p < 0.01) [39]. This suggests that the decision to allocate two organs simultaneously to a single recipient requires careful patient selection to ensure the best possible outcomes. The most important survival benefit after HKT is an increase in cardiac graft survival. UNOS data analysis shows that while 1-year survival is similar, 5- and 10-year cardiac graft survival is significantly better in HKT compared with HT patients.17. Actually, our series proved that concept, showing 88% of conditional survival at 7 years. Multiple reports show significantly lower rates of cardiac allograft rejection in HKT compared with HT. The etiology of "immune paralysis" is based on the inclusion of a much higher antigenic load with dual solid organs resulting in partial tolerance leading to fewer rejection events [38,40]. This could possibly be responsible for not only reduced acute rejection episodes but also for decreased CAV rates and therefore lead to improved cardiac allograft survival in HKT patients. Our incidence of rejection were just 10 events during this 7-year period of follow-up, and just 25% developed CAV.

Abut the renal outcomes it is imperative to keep in mind that kidneys that are allocated to multiorgan transplant recipients are ahead of those requiring KT, ergo, those grafts are generally of higher quality. However, in redirecting better organs to recipients with shorter life expectancies, HKT may lead to decreased renal allograft lifespan. As we described before, HKT is associated with improved renal and survival outcomes compared with HT in patients with impaired renal function. However, when comparing overall survival in separate populations, HKT patients have increased in-hospital mortality, resulting in reduced 1-year survival rates compared with all KT patients [41]. This also increase the per se high complexity of this multiorgan thoracic transplant. On our series, just one patient (12%) developed severe primary graft dysfunction of the heart, and one patient required dialysis in the first 48 postoperative; he recovered the renal function, but eventually had irreversible renal graft failure 3 years later. Overall, we can conclude that the evidence suggests that utilization of kidney allografts for HKT patients is appropriate, with care taken to identify patients at increased risk of poor outcomes.

Finally, MOT has risen considerably over the past two decades, and up to 90% include a kidney. Simultaneous HKT is an established therapy for end-stage heart and renal failure. Outcomes are highly favorable, with excellent overall and allograft survival, especially with GFR < 30 ml/min/1.73 m2. The most important survival benefit after HKT and HLT is an increase in cardiac graft survival. HLT is an accepted treatment modality for selected patients with end-stage cardiac and pulmonary failure. The number of HLT performed in the United States has drastically increased in recent years. Although the experience with ECMO as a BTLT is limited results are encouraging, despite significant morbidity, allows to successfully bridge patients to transplantation with excellent clinical outcomes.

Ambulation and physical rehabilitation in patients on ECMO support is safe and can potentially improve post-trans-

plant recovery and outcomes. Even when mortality after HLT has decreased, morbidity has remained relatively constant, and is generally due to malignancies, infections, and chronic allograft dysfunction.

FUNDING: None

DISCLOSURE: The authors have no conflicts of interest to disclose.

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