Ten-year follow-up in patients with combined heart and kidney transplantation

Gregory D. Trachiotis, MD^a

J. David Vega, MD^a

Thomas S. Johnston, MD^b

Alex Berg, RN^b

John Whelchel, MD^c

Andrew L. Smith, MD^b

Jerry Lutz, MD^b

Kirk R. Kanter, MD^a

Dr Trachiotis

Background: Combined heart and kidney transplantation has been documented, although data regarding immunosuppression, rejection episodes, and graft or patient survival have not been detailed. We evaluated our experience and more than 10-year outcome with patients selected for combined heart and kidney transplantation.

Methods: Eight patients aged 29 to 59 years were selected for combined heart and kidney transplantation. The indications were end-stage heart disease and underlying renal pathology, or secondary renal insufficiency, or renal failure. Six patients were dialysis dependent before transplantation. There were 7 simultaneous procedures and 1 staged procedure. The heart was transplanted first in all cases. All patients were maintained after transplantation on azathioprine ($2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) and whole-blood monoclonal cyclosporine levels at greater than $200 \mu\text{g/L}$; prednisone was not decreased to less than 10 mg/d.

Results: Seven (87.5%) patients have survived a mean duration of 100.4 months (range, 51-144 months), and each allograft has continued to function. The only death was due to pulmonary emboli and was not related to allograft rejection or failure. Only 4 cardiac and 4 kidney allograft rejections have occurred. Five patients have been free of kidney rejection, 1 patient has been rejection free for more than 8 years, and no patient has had simultaneous rejection.

Conclusions: In select patients, combined heart and kidney transplantation can provide long-term graft function and patient survival. The low rates of rejection support our current approach to immunosuppression. Our experience indicates that end-stage failure of either heart or kidney does not necessarily preclude dual-organ transplantation.

From the Divisions of Cardiothoracic Surgery,^a Cardiology,^b and Kidney Transplantation,^c Emory University, Atlanta, Ga.

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Address for reprints: Gregory D. Trachiotis, MD, The Division of Cardiovascular and Thoracic Surgery, Sec 112, The George Washington University Medical Center/Veterans Affairs Medical Center, 50 Irving St, NW, Washington, DC 20422 (E-mail: grachiotis@mfa.gwu.edu).

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Heart and kidney transplantation has made great progress in the cyclosporine era. At our institution, patient 1-year survivals for heart and kidney (HTK) transplant recipients are 93% and 98.4%, respectively. Coupled with the growing successes in individual solid organ transplantation, there has also been an increase in the number of multiple organ transplants, such as pancreas/kidney, heart/lung, heart/liver, and liver/kidney.¹⁻⁵ This trend has been in part due to a better understanding of immunobiology, advances in surgical technique and postoperative care, and an often-common pathologic association between dual-organ failure. This pathologic course is exemplified for end-stage heart failure leading to secondary renal dysfunction or failure, or for end-stage renal failure as a cause for (uremic) cardiomyopathy. However, refractory cardiac failure has long been considered a

TABLE 1. Patient demographics and clinical characteristics

Patient no.	Age (y)	Sex	Heart disease	Kidney disease	EF (%)	Dialysis	LVAD
1	44	M	ICM	PCD	23	Yes	No
2	49	M	ICM	HTN	14	No	No
3	48	M	AL CM	ATN*	30	No	Yes
4	36	M	IDCM	ATN*	15	Yes	No
5	29	M	IDCM	HTN	18	Yes	No
6†	59	M	IDCM	ATN*	17	Yes	No
7	53	M	IDCM	PCD‡	15	Yes	No
8	44	F	IDCM	Auto HTN	10	Yes	No

ATN, Acute tubular necrosis; AL CM, alcohol cardiomyopathy; Auto, autoimmune; EF, ejection fraction; F, female; HTN, hypertension; ICM, ischemic cardiomyopathy; IDCM, idiopathic cardiomyopathy; LVAD, left ventricular assist device; M, male; PCD, polycystic kidney disease.

*ATN was caused by consequences of end-stage heart failure.

†This patient had a staged kidney transplantation 2 years after complications from a previous heart transplantation.

‡PCD was the primary disease, but the patient required a second kidney transplantation after allograft failure 7 years earlier.

contraindication to kidney transplantation. Additionally, cardiac transplantation has been denied for patients with end-stage renal disease. Over recent years, combined HTK transplantation has been offered to select patients who were once denied transplantation.

There have been several case reports and small series documenting the feasibility of performing either simultaneous or staged HTK transplantation.⁶⁻¹⁵ However, long-term data regarding immunosuppression protocols, rejection profiles, and graft and patient outcomes have not been detailed. We report a single-institutional experience with combined HTK transplantation with follow-up extending beyond 10 years.

Patients and Methods

From January 1990 to March 1998, 8 patients with a mean age of 45.9 years (range, 29-59 years) underwent combined HTK transplantation. Each patient met standard criteria for orthotopic heart transplantation initially and was then deemed an acceptable candidate for kidney transplantation. Primary heart or kidney disease as an etiology for dual-organ failure was not an exclusion criterion, but difficult-to-manage diabetes, diabetic retinopathy or neuropathy, extensive peripheral vascular disease, or age older than 60 years were reasons for exclusion. The etiology of end-stage heart failure was idiopathic cardiomyopathy ($n = 5$), ischemic cardiomyopathy ($n = 2$), and alcohol cardiomyopathy ($n = 1$). Each patient had severe fixed impairment of systolic cardiac function with an average ejection fraction of 17.8% (range, 10%-23%) and New York Heart Association class III or IV symptoms. Renal failure or dysfunction was caused secondary to primary cardiomyopathy ($n = 4$), polycystic kidney disease ($n = 2$), and autoimmune disorder ($n = 1$) or secondary to multisystem organ failure after cardiac transplantation ($n = 1$). Six of these patients had irreversible end-stage renal failure managed by dialysis. In 1 of these patients, hemodialysis-dependent renal failure developed after insertion of a left ventricular assist device for decompensating heart failure. Two other patients had severe renal dysfunction with an average glomerular filtration rate (GFR) of 34 mL/min and an average creatinine level of 2.6 mL/dL on maximal medical

therapy for heart failure. The patient profiles are summarized in Table 1.

Donors were matched for each recipient on the basis of donor and recipient weight, recipient transpulmonary gradient, and ABO blood group identity. The immunologic profiles are listed in Table 2. Selection was not based on prospective HLA antigen matching except for the 1 staged procedure, for which the 2 most recent candidates had documented panel-reactive antibodies $>20\%$. Routine retrospective lymphocytotoxic cross-matching was performed and available hours after implantation.

The donor organs were procured and implanted by members from the Emory University transplant team. At the time of procurement, each heart was perfused and stored at 4°C in 1 L of Roe cardioplegic solution. The kidneys were perfused en bloc with other abdominal organs with University of Wisconsin solution and stored at 4°C in 1 L of University of Wisconsin solution. The heart was implanted first in all cases. After the patient was weaned from cardiopulmonary bypass and hemodynamic stability was attained, heparin was reversed and hemostasis was achieved, and then the chest was closed and drained. Kidney implantation was then performed without delay in standard fashion. All patients were managed jointly in the cardiovascular surgical intensive care unit, although each patient remained under the direct care of the heart transplant team until discharge.

Preoperative immunosuppression consisted of cyclosporine 2 to 3 mg/kg, azathioprine 3 to 4 mg/kg, and methylprednisolone (Solu-Medrol) 500 mg intravenously (IV). Thereafter, immunosuppression was maintained with whole-blood cyclosporine (INN: ciclosporin) levels of more than 200 $\mu\text{g/L}$, azathioprine 2 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$, and methylprednisolone 125 mg IV every 8 hours for 6 doses. Prednisone was then started at 1 $\text{mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ in divided doses; it was weaned by 5 mg/d to 20 mg/d and then to a maintenance dose of 10 mg/d over the subsequent 6 to 12 months.

Rejection was monitored in the case of hearts by surveillance endomyocardial biopsies (EMB) commencing on day 7, then weekly for 4 weeks, twice monthly for 3 months, monthly until 6 months, and then every 2 months until 1 year. Patients underwent EMB every 3 months until year 2, and then they had an EMB once or twice yearly or in cases of suspected graft rejection. For the kidneys, rejection was generally monitored by noninvasive means,

TABLE 2. Immunologic profile

Patient no.	PRA (%)	Cross-match	HLA		HLA mismatch (AB/DR)	Ischemic time (min)	
			Recipient	Donor		Heart	Kidney
1	0	Negative	A: 24, 29; B: 27, 44; DR: 4, 7	A: 1, 2; B: 8, 57; DR: 3, 7	4/1	121	556
2	0	Negative	A: 26, 28; B: 14, 53; DR: 7, 8	A: 2, 33; B: 14, 60; DR: 12	3/2	58	306
3	0	Negative	A: 2, 25; B: 7, 44; DR: 4, 13	A: 2, 28; B: 44, 60; DR: 11, 15	2/2	32	Living related
4	N/A	Negative	A: 2, 28; B: 60, XX; DR: 8, XX*	A: 3, 11; B: 44; DR: 1, 11	4/2	54	244
5	0	Negative	A: 2, 28; B: 58, XX; DR: 12, XX	A: 1, 24; B: 38, 60; DR: 1, 7	4/2	75	296
6	0	Negative	A: 3, 30; B: 7, 35; DR: 1, 11	A: 3, XX; B: 7, 35; DR: 7, 15	1/2	123	1093
7	44/0	Negative†	N/A	N/A	N/A	159	560
8	20	Negative†	N/A	N/A	N/A	128	380

PRA, Panel-reactive antibody; N/A, not applicable.

*XX represents unidentified HLA typing and was regarded as a mismatch.

†These patients were prospectively HLA typed because of increased PRA. Even though patient 7 was able to have the PRA reduced with dithiothreitol, there was a history of kidney allograft loss.

including serum creatinine levels, but it was always documented by graft kidney biopsy. Allograft kidney biopsy or cardiac biopsy was not performed empirically in cases of isolated single allograft rejection.

Infection prophylaxis against *Pneumocystis carinii* pneumonia consisted of a daily co-trimoxazole (Bactrim DS) tablet. In general, no prophylaxis was given for cytomegalovirus unless a positive seroconversion, infection, or disease was documented from shell-vial or polymerase chain reaction analysis. Therapy consisted of IV ganciclovir therapy (5 mg/kg every 12 hours); the duration of treatment varied throughout the study period. Follow-up care was maintained in cooperation between the HTK transplant teams. Survival was determined by the Kaplan-Meier method.

Results

The rejection profiles, clinical results, and outcomes are summarized in Table 3. There was 7 simultaneous HTK transplantations and 1 staged HTK transplantation. The donor was the same in 6 of 7 simultaneous transplantations; the other was a living related kidney donor. The mean ischemic time for the cardiac allografts (n = 8) was 93.8 ± 42 minutes, and for the kidney allografts (n = 7) it was 470.7 ± 271 minutes. There were no intraoperative or perioperative complications.

There was only 1 cardiac allograft rejection episode (International Society of Heart and Lung Transplantation [ISHLT] grade >2) in each of 4 patients, and there were 2 kidney allograft rejection episodes in each of 2 patients. The range for the time to first cardiac rejection was 5 to 34 months, and for kidney rejection it was 1 and 37 months. All rejection episodes responded to standard therapy. Moreover, there has not been a documented cardiac allograft rejection since April 1995 or a kidney allograft rejection since Jan-

uary 1995. Five patients are free of kidney rejection, 1 patient has been rejection free for more than 6 years, and no patient has had simultaneous HTK rejection. Therefore, there have been a total of 8 rejection episodes in a total cumulative follow-up period of 694 graft-months in surviving patients.

Cardiac complications in follow-up have been bradycardia requiring a DDD pacemaker (n = 2), hypertension requiring augmentation of therapy (n = 2), and cardiac allograft dysfunction unrelated to coronary vasculopathy (leading to subsequent staged kidney transplantation; n = 1). Renal allograft complications have been renal insufficiency secondary to hypertension, cyclosporine, or both (n = 1) and urinary tract infection (n = 1). All kidney allografts are functioning; the mean GFR in the surviving patients is 65 ± 15 mL/min. There has been no significant coronary vasculopathy in any patient, but 1 patient had a 50% diameter left anterior descending artery occlusion. The cardiac function has remained normal in 6 of 7 surviving patients, the mean ejection fraction for these patients has been $56\% \pm 13\%$, and all patients are New York Heart Association class I or II. Early or late infections with cytomegalovirus have not been a concern.

Seven (87.5%) of 8 patients have survived a mean of 100.4 ± 38.7 months (range, 51-144 months) with 100% graft survival. The patients' cumulative survival at 30 days and 1 year was 100% and 87.5%, respectively (Figure 1). Five patients thus far have lived beyond 5 years, and the patient who has survived longest has lived beyond 12 years. The 1 patient death occurred 31 days after simultaneous transplantation because of pulmonary emboli and was not related to allograft rejection or failure.

Figure 1. Actuarial survival for simultaneous heart/kidney transplantation.

TABLE 3. Rejection profile and outcome data

Patient no.	Rejection		Adverse event	EF (%)	GFR > 50 (mL/min)	Survival	Follow-up (mo)
	Heart	Kidney					
1	1	2	HTN	60	Yes	Alive	144
2	1	0	Pacemaker	60	Yes	Alive	138
3	0	0	None	65	Yes	Alive	97
4	0	0	PE	N/A	Yes	Death	1
5	1	2	HTN, renal insufficiency	55	No	Alive	90
6	1	0	Pacemaker	25	Yes	Alive	130
7	0	0	UTI	65	Yes	Alive	51
8	0	0	None	60	Yes	Alive	53

GFR, Glomerular filtration rate; HTN, hypertension; PE, pulmonary emboli; UTI, urinary tract infection; EF, ejection fraction; N/A, not applicable.

Discussion

The documentation of successful combined HTK transplantation continues to grow.⁶⁻¹⁵ In a corroborative report using data from the ISHLT and United Network for Organ Sharing, there were 84 simultaneous HTK transplantations performed between 1987 and 1995, with a mean follow-up of 2 years.³ A wider application of HTK transplantation in the current arena of scarce donor resources may not be fully realized until long-term outcome data are available documenting patient and graft survival comparable to those with single-organ transplantation. Although clinical experience with heart transplantation has allowed expansion of selection criteria, patients with end-stage heart disease and chronic renal dysfunction are generally excluded from single cardiac transplantation. Additionally, patients with end-stage renal failure with concomitant severe cardiac dysfunction are refused kidney transplantation. As the waiting lists for heart or kidney transplantation continue to increase, the potential for second-organ dysfunction that requires consideration for multiorgan transplantation may occur in larger proportions. The kidney remains the most vulnerable extrathoracic organ in patients awaiting heart transplantation.

Patients with either organic kidney disease (eg, polycystic kidney disease) or intrinsic renal disease as a consequence of systemic conditions (eg, hypertension or diabetes) have the added burden of a low cardiac output, which can lead to or potentiate renal dysfunction.¹⁶ The rationale for inclusion of patients for simultaneous transplantation who have both cardiomyopathy and dialysis-dependent renal failure or pathologic kidney disease (eg, polycystic kidney disease) is more evident than in those patients who have a primary cardiomyopathy and secondary renal insufficiency or dysfunction. In the ISHLT registry, approximately 20% of patients selected by criteria for heart transplantation alone had some component of renal insufficiency at 1 year.³ Moreover, in one report, 55.3% of patients with pre-heart transplantation creatinine greater than 1.5 mg/dL had chronic renal insufficiency, and for this subgroup, 28.5% became dialysis dependent.¹⁶ The cause of renal insufficiency has been attributed to the adverse effects of cyclosporine and glucocorticoids,¹⁷⁻¹⁹ because hypertension, hyperlipidemia, and diabetes occurred in 18% to 67% of these same patients by 1 year.³ Cases of dialysis-dependent renal failure due to long-term cyclosporine toxicity can also oc-

cur, although this is an extremely unusual event in our experience and according to the ISHLT registry.³ If this has occurred, it has usually been associated with a complicated event, as in one of our cases. Therefore, it is our opinion that optimally managed patients with end-stage heart failure who have a serum creatinine greater than 1.8 mg/dL and a GFR less than 40 mL/min are at high risk of becoming dialysis dependent after heart transplantation and are potentially more suitable candidates for an HTK transplantation, as were 2 of the patients in this study.

In our series, except for the 1 staged procedure, no attempt was made to perform prospective HLA matching. Although HLA matching has been shown to be advantageous not only for renal, but also for cardiac, allograft survival,^{20,21} this type of prospective testing has not been feasible in efforts to minimize cardiac ischemia. However, the very short cold ischemia time of the kidney in the simultaneous procedure is a significant technical advantage of the double procedure when compared with single cadaveric kidney grafting, in which long cold storage is associated with poor early function and reduced long-term graft survival.²² Whether limiting the ischemic time provides an immunologic advantage is unclear. However, with the selection of donor and recipient matching based on ABO typing and low panel-reactive antibody results and with the relatively short donor ischemic times, the early and long-term rejection profiles of the simultaneous HTK recipients in our report have been excellent. We also believe that surveillance EMB, pathologic documentation of heart or kidney rejection, careful follow-up, and, in particular, the immunosuppressive regimen have been important elements in our management strategy. In contrast to our heart transplantation population, which undergoes routine weaning of immunosuppressive therapy, whole-blood cyclosporine levels are maintained at greater than 200 μ g/L, and prednisone is not weaned after 6 months but is kept at 10 mg/d in the HTK recipients. This philosophy is different from that with isolated heart or kidney transplantation, in which prednisone is attempted to be completely weaned after the initial 6 months after transplantation if there has not been a rejection episode. Also, since 1998, for isolated heart or kidney transplantation, we have used mycophenolate mofetil in place of azathioprine in our 3-drug regimen, which has allowed for more patients to be weaned from steroids. For future HTK transplantations, we will use mycophenolate mofetil in place of azathioprine and may consider weaning patients off steroids if the rejection profiles remain low. Nonetheless, from our heart transplantation experience, we do have some reservations regarding steroid weaning. We have found that even as long as 7 years after heart transplantation, 7.4% of patients will sustain a grade 2 or higher rejection, and even at a mean follow-up at 4 years, only 50% of heart transplant recipients will be free from acute rejection.

Whether the advent of newer typing techniques using DNA methodology for HLA class I or II typing within 2 to 4 hours on lymphocytes obtained antemortem from the donor to allow better HTK matching will affect this immunosuppressive strategy remains to be seen.

Another interesting concept is to speculate whether rejection in these patients has been attenuated by an altered immune response to dual-organ transplantation.^{10,12,15} For example, it is widely recognized that simultaneous pancreas and kidney transplantation results in higher pancreas survival than if the pancreas is transplanted alone.²³ Also, in heart/lung transplant recipients, cardiac rejection is far less common than pulmonary rejection.^{2,24,25} Additionally, in combined heart/lung transplant recipients, pulmonary grafts tend to respond more rapidly to antirejection therapy than isolated cardiac grafts.²⁵ These observations likely occur because, in the simultaneous setting of organ or tissue transplantation, the recipient immune cells do not produce cytokines critical for clonal activation, expansion, and amplification of alloresponses, a term named the *combi effect*.²⁶ In contrast, for our heart transplant patients, approximately 30% will have a grade 2 or higher rejection within the first year, and although this percentage decreases with time, the risk is still present at 7 years. Also, our graft survivals for isolated cardiac grafts at 1, 5, and 10 years were 91%, 74.3%, and 52.3%, respectively, and for kidney grafts at 1, 5, and 10 years they were 95%, 73%, and 44%, respectively. In our 7 surviving HTK transplant recipients, graft survival is 100% at a mean follow-up of 9 years. With this report, although rejection for HTK transplantation occurs within the first year, it is infrequent and not refractory, and after 1 year it is virtually absent; this implicates the role of dual-organ transplantation as a mechanism for immune tolerance. The role that multiorgan transplantation may play in extending graft acceptance and patient survival and how it may alter or enhance our approaches to chemical immunosuppression remain to be defined by future clinical investigation and research.

The complications from long-term immunosuppression are well documented^{3,17,18,27} but fortunately have not been a significant treatment issue with our patients. Hypertension is commonplace in cyclosporine-managed renal allografts and develops after heart transplantation as well.^{3,27} Because cyclosporine-induced hypertension can yield fixed systemic vascular disease,^{17,27} we liberally manage patients with a calcium channel blocker, most recently with amlodipine at 5 to 7.5 mg/d. The potential advantages of using a calcium channel blocker with HTK transplants are that calcium channel blockers have the following effects on HTK allografts: (1) They improve early renal allograft function; (2) they preserve long-term renal function in cardiac allograft recipients; (3) they provide potential long-term protection from coronary vasculopathy in cardiac allografts; (4) they

allow for lower doses of cyclosporine based on the stimulatory effects on the P450 system; and (5) they improve antihypertensive effects.^{28,29} Only 2 of 5 patients have developed hypertension long-term that has required increased doses of amlodipine or the use of adjunctive agents. Also, all patients are maintained on statin therapy, and pravastatin (Pravachol) (10-20 mg/d) is the cholesterol-lowering agent of choice because of its favorable drug interactions and pharmacokinetics with immunosuppressive agents. To this end, diabetes, peripheral vascular disease, hyperlipidemia, or significant coronary vasculopathy have not occurred in the surviving patients.

One potential limiting factor to a wider application of simultaneous HTK transplantation is the lower yield of usable hearts to kidneys from a single donor, thereby increasing the waiting time for these chronically ill patients. It is feasible to manage patients for longer periods on the waiting list for HTK transplantation with chronic hemodialysis until a suitable donor becomes available. We currently have patients on our waiting list who fall into this category. One alternative for this subgroup of patients, as illustrated by one of the patients in this report, is to use a cadaveric heart donor and a living related kidney donor. Additionally, in the future, with wider application of mechanical assist devices, there may be the development of renal failure on left ventricular assist device support,³⁰ as in one of our patients, and this necessitates HTK transplantation. Thus, as the number of patients with end-organ failure, especially coexisting cardiac and kidney failure, increases, our consideration to treat these patients by dual-organ transplantation must broaden and be flexible.

In this report, we have confirmed the safety, efficacy, and long-term success of HTK transplantation in a small number of patients with failure of both organs. The HTK transplantation procedure, however, is lengthy and potentially increases the technical risks of surgery. Transplant programs that wish to expand to multiorgan transplantation should have an established track record in isolated cardiac and abdominal transplantation, preferably performing more than 20 isolated transplantations per year, and have a multidisciplinary team for these particular patients. Also, critical to the success of the procedure and to the long-term management is cooperation between the 2 transplant disciplines. Our current approach to patient selection, treatment, and immunosuppression is supported by low rates of rejection and long-term graft and patient survival. Our experience suggests that end-stage failure of either the heart or kidney does not necessarily preclude patients from dual-organ transplantation.

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