Objectives: Combined heart-kidney transplantation with allografts from the same donor has been long proved to be a feasible approach for selected patients with coexisting end-stage cardiomyopathy and renal disease. The purpose of this retrospective study is to analyze our long-term results and compare these results with heart-only transplantation over a 7-year period.

Methods: Between June 1992 and April 1999, 10 patients underwent combined heart-kidney transplantation at Cedars-Sinai Medical Center. They were all men from 44 to 70 years old (mean age, 59 ± 8.3 years) who had a mean left ventricular ejection fraction of 19.4% ± 5.0% (range, 9%-25%) and a mean creatinine clearance of 25.4 mL/min (range, 10-39 mL/min). Four patients underwent pretransplantation dialysis.

Results: There was no operative mortality. The actuarial survival at 1, 2, and 5 years was 100%, 88% ± 11.7%, and 55% ± 20.1%, respectively. By comparison, the operative mortality of 169 patients who underwent heart-only transplantation during the same time interval was 2.4%, with an actuarial survival at 1, 2, and 5 years of 92% ± 2.1%, 84% ± 2.8%, and 71% ± 3.9%, respectively (P = .37). Eight patients showed no evidence of significant (≥1B) cardiac allograft rejection postoperatively, and the actuarial freedom from rejection at 30 days, 1 year, and 2 years was 90% ± 9%, 80% ± 13%, and 80% ± 13%, respectively. Renal allograft survival was 90% at 1 and 2 years.

Conclusions: Combined heart-kidney transplantation yields satisfactory long-term results similar to those for heart-only transplantation, with a low incidence of cardiac allograft rejection and renal allograft survival when both allografts are from the same donor. This approach effectively expands the selection criteria for heart-only and kidney-only transplantation in potential candidates with coexisting end-stage cardiac and renal disease.
Combined heart-kidney transplantation, although infrequently performed, has become an accepted therapeutic option for patients with end-stage heart disease associated with severely impaired renal function. Experience with this combined approach has shown that the presence of abnormal renal function does not preclude heart transplantation, provided there are no signs of other organ failure. Conversely, the presence of severely impaired cardiac function in patients with end-stage renal disease no longer presents a contraindication for kidney transplantation if they are otherwise good candidates.

Our initial experience with this cohort of patients was reported in 1994 and included 3 patients who underwent combined heart-kidney transplantation with allografts from the same donor. Encouraged by our results, we have pursued this approach in 10 patients who form the basis of this report. This retrospective analysis focuses on the lessons learned, particularly regarding patient and donor selection, postoperative management, and surveillance, as well as long-term patient and allograft outcome.

**Materials and Methods**

Between June 1992 and April 1999, 169 patients underwent heart transplantation, 393 patients underwent kidney transplantation, and an additional 10 patients underwent combined heart-kidney transplantation at Cedars-Sinai Medical Center. The preoperative characteristics are shown in Table 1. The cause of renal disease is shown in Table 2, and the preoperative renal function and dialysis status are shown in Table 3. Only 1 patient was undergoing dialysis at the time of listing for transplantation (having undergone an unsuccessful kidney transplant previously), and 3 additional patients began dialysis while awaiting transplantation. Donor heart characteristics are presented in Table 4, and intraoperative characteristics are provided in Table 5.

Our criteria for renal transplantation along with cardiac transplantation included a creatinine clearance of less than 40 mL/min and a serum creatinine level of more than 2.0 mg/dL, despite hemodynamic optimization with intravenous inotropic and vasodilator agents measured on at least 2 occasions.

All patients underwent combined heart-kidney transplantation with a staged approach; namely, the renal allograft implantation was delayed to a second operative procedure a few hours after cardiac transplantation to allow for hemodynamic stabilization and correction of coagulation abnormalities if present. Although no post-transplantation renal biopsies were performed to diagnose acute rejection episodes, the function of the transplanted kidney in the early postoperative period was followed by serial renal duplex scans measuring parenchymal blood flow for resistance index, renal arterial and venous flow signal, and color Doppler perfusion to assess allograft size.

Data were summarized by means of frequencies and percentages for categorical variables and means and standard deviations for continuous variables. Survival probabilities were calculated with the actuarial method of estimation. The life-table method by means of Kaplan-Meier analysis was used to construct survival curves.

Immunosuppressive therapy consisted of OKT3 induction therapy (5 mg administered intravenously daily) maintained for 7 days in the first 6 patients. The remaining 4 patients received antithymocyte globulin (15 mg/kg daily adjusted for white blood cell and platelet counts) for 7 days. Maintenance immunosuppressive therapy consisted of cyclosporine (INN: ciclosporin; 5 mg · kg⁻¹ · d⁻¹), for a level of 200 to 400 ng/mL, as measured with a monoclonal fluorescence polarization immunoassay within the first 12 weeks after transplantation and for a level of 120 to 200 ng/mL thereafter, started postoperatively once the serum creatinine level was less than 2.0 mg/dL; azathioprine (4 mg/kg preoperatively and 2 mg · kg⁻¹ · d⁻¹ postoperatively adjusted to the patient’s white blood cell and platelet count) later switched to mycophenolate mofetil (1000 mg twice daily) for all patients as of January 1997; and steroids (methylprednisolone sodium succinate, 1 g at removal of aortic cross-clamp intraoperatively and then 125 mg intravenously every 8 hours for 3 doses postoperatively, followed by prednisone, 0.25 mg · kg⁻¹ · d⁻¹, during OKT3 or antithymocyte globulin therapy, increased to 0.5 mg · kg⁻¹ · d⁻¹, and then tapered off in the subsequent 3 to 8 months). Endomyocardial biopsies were performed according to our surveillance protocol or when acute cardiac rejection was clinically suspected. Cardiac rejection episodes were treated if greater than 1B, according to the classification of the International Society for Heart and Lung Transplantation. Renal allograft rejection was suspected by means of indirect serum biochemical measurements of renal function and by means of Doppler ultrasonographic resistance index–perfusion scan techniques and treated accordingly.

**Results**

The 30-day operative mortality was 0%, and actuarial survival at 1, 2, and 5 years was 100%, 88% ± 11.7%, and 55% ± 20.1%, respectively. By comparison, the operative mortality of 169 patients who underwent heart transplantation in our institution during the same period of time was 2.4%, with an actuarial survival at 1, 2, and 5 years of 92% ± 2.1%, 84% ± 2.8%, and 71% ± 3.9%, respectively (P = .37, Figure 1). Renal allograft survival was 90% at 1 and 2 years. However, no statistically significant prediction of the 5-year renal allograft survival could be made because of the small number of patients with a 5-year follow-up (Figure 1).

Postoperative renal function is shown in Table 6. Diuresis caused by the well-functioning kidney allograft was observed soon after transplantation in all patients, which avoided the need for post-transplantation dialysis. The serum creatinine level fell below 2.0 mg/dL in all patients within 7 to 10 days after transplantation. Renal complications in the post-transplant period included one episode of acute tubular necrosis caused by cyclosporine toxicity at 30 days that resolved without the need for dialysis and without observed improvement in the patient’s native renal function. A second patient had an episode of severe acute rejection with renal parenchymal infarct that
required allograft nephrectomy 30 days after transplantation. (The patient’s native renal function only partially recovered after transplantation but eventually deteriorated and required dialysis 1 year later.) In contrast, of the 169 patients who underwent heart-only transplantation during the same study time interval and who had a creatinine clearance greater than 40 mL/min and a serum creatinine level below 2.0 mg/dL, only 1 patient required renal transplantation (living related) for deteriorating renal function 5 years after heart transplantation. In addition, 2 other similar patients were placed on permanent dialysis 4 and 5 years after heart transplantation, respectively, and are awaiting kidney transplantation. However, an additional 14 patients with similar preoperative characteristics have demonstrated deteriorating renal function with a serum creatinine level between 2.5 and 3.5 mg/dL in the late postoperative period. The actuarial freedom from cardiac allograft rejection (International Society for Heart Lung Transplantation classification, ≥1B) at 30 days, 1 year, and 2 years was 90% ± 9%, 80% ± 13%, and 80% ± 13%, respectively. Only 2 patients showed a single episode of cardiac rejection (≥1B) on endomyocardial biopsy, one graded 3A at 30 days and another graded 3B at 60 days, which resolved with pulsed-steroid therapy. Three patients died in the follow-up period: one patient died of transplant atherosclerosis at 24 months; a second patient died of complications of renal failure–dialysis (with an explanted renal allograft) at 28 months; and a third patient died of interstitial pneumonitis at 54 months.

**Discussion**

Although combined heart-kidney transplantation with allografts from the same donor has been long proved to be a feasible therapeutic option, it is rarely performed. The United Network for Organ Sharing Registry reports 165 such combined organ transplantations performed between 1988 (when the United Network for Organ Sharing began collecting transplantation data) and 1999. During the same period of time, 25,952 heart and 126,132 kidney transplantations were performed in the United States, and combined heart-kidney transplantation represents 0.6% and 0.1% of the total heart and kidney transplantation experiences, respectively, during the same period of time. In our institution 286 patients have undergone heart transplantation, and 962 patients have undergone kidney transplantation, whereas only 10 such combined procedures have been performed. At present, 1- and 5-year survivals of 82% and 65%, respectively, can be expected for heart transplantation. The current 1- and 5-year patient survivals for cadaveric kidney transplantation are 94% and 82%, with expected 1- and 5-year allograft survivals of 84% and 62%, respectively. Even higher survival are expected for living-related kidney transplantation. This success in single-organ transplantation has been translated into expanded indications for heart and kidney transplantation.

Since the initial report of simultaneous heart-kidney transplantation with allografts from the same donor in 1978, multiple solid-organ transplantation has evolved into

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**TABLE 1. Preoperative patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at transplantation (y)</td>
<td>59.0 ± 8.3</td>
<td>44-70</td>
</tr>
<tr>
<td>Male sex</td>
<td>10 (100%)</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic</td>
<td>7 (70%)</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>3 (30%)</td>
<td></td>
</tr>
<tr>
<td>NYHA class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>3 (30%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>7 (70%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (50%)</td>
<td></td>
</tr>
<tr>
<td>Creatinine level (mg/dL)</td>
<td>4.05</td>
<td></td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>25.4</td>
<td></td>
</tr>
<tr>
<td>Previous operations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CABG</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>AVR</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Transplant status (UNOS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6 (60%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>4 (40%)</td>
<td></td>
</tr>
<tr>
<td>Waiting time to transplant (d)</td>
<td>197 ± 201</td>
<td>14-700</td>
</tr>
</tbody>
</table>

SD, Standard deviation; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; AVR, aortic valve replacement; UNOS, United Network for Organ Sharing.
an acceptable approach with satisfactory short and interme-
diate results. Although the long-term results of combined
heart-kidney transplantation are not known yet, the
observed survival trend matches the rates for heart and kid-
ney transplantation and is associated with a lower inci-
dence of rejection in both allografts.1,5,12 This decreased rejection
rate is intriguing and occurs despite the fact that heart-kid-
ney transplant patients receive randomly HLA-matched
hearts and kidneys, as do heart-only recipients. Although the
effects of poor or no HLA matching on long-term combined
heart-kidney transplant recipients is uncertain, it appears
that HLA incompatibility is not associated with rejection
but does affect the survival.13 However, other studies have
shown that the number of HLA mismatches predicts not
only the rejection rate but also the mortality rate after heart
transplantation. HLA-B antigen mismatch, and particularly
2 HLA-DR antigen mismatches, are associated with a higher
rejection rate and a stronger immune response.14,15
Optimal HLA compatibility, particularly HLA-DR, reduces
the strength of the immune response in kidney transplanta-
tion and is associated with a greater long-term patient and
allograft survival.14,16,17 Even though no HLA matching is
performed in heart or combined heart-kidney transplantation,
although it is routinely used in kidney transplantation in
our institution, the low incidence of rejection in our series
of heart-kidney transplantation and in previously published
reports is noteworthy. It has been long observed in exper-
imental animals that multiple transplanted organs from the
same donor protect each other immunologically. This sug-
gests that any organ transplant combination may induce
graft tolerance or reduce host immunoresponsiveness,
although the validity of this immune event in human
patients is not clearly known.18
A second advantage of using allografts from the same
donor is the avoidance of further antigenic stimulation and
immunologic burden because a second unrelated allograft
with different HLA typing might further enhance the recip-
ient’s immune response (ie, living-related kidney donor
because it implies 2 different donors for combined heart-
kidney transplantation).
It has also been observed that the incidence of graft tol-
erance is increased in patients who have received multiple
allogenic transfusion before renal transplantation, perhaps
caused by specific T-cell tolerance.19 Because the quantita-
tive presence of major histocompatibility complex class I
and class II antigens in the kidney is 14- and 18-fold higher
than in the heart, respectively, it is possible that the coexis-
tence of an organ with quantitatively higher but qualita-
tively similar antigenic determinant may help induce immune
tolerance to the organ with lower antigenic expression.5,20
This is supported by the lower incidence of rejection
observed in other combinations of solid-organ transplanta-
tion, such as heart-lung and kidney-pancreas transplanta-
tion.21,22 It has been suggested that hematopoietic stem cells
from the allograft migrate to the recipient’s bone marrow
and other lymphoid organs. The coexistence of the allograft
cells with the recipient’s precursor stem cells may result in
the development of spontaneous chimerism perpetuated by
the mutual cell engagement of donor and host leukocytes.
This interaction may lead to the stimulation of suppressor T cells, with a mutually inhibitory immune response between the host and the allograft. This may be further enhanced by the presence of an immunosuppressive agent, such as cyclosporine or an anti-CD4 agent, with a resultant immunotolerance rather than rejection. In addition to the low incidence of rejection, it has been noted that simultaneous rejection of cardiac and renal allografts are rare and that the occurrence of rejection in combined heart-kidney transplantation is independent in each allograft. Thus, monitoring of rejection must be carried out separately for each transplanted organ. The observed incidence, albeit low, of rejection episodes in heart-kidney transplant patients is slightly higher in the cardiac allograft than in the renal allograft. It is possible, however, that this may be due in part to the histopathologic need to confirm the presence of cardiac rejection rather than using the indirect biochemical techniques, Doppler ultrasound diagnostic techniques, or both, to confirm renal allograft rejection. Because renal biopsy specimens are rarely performed to diagnose rejection, perhaps an undefined number of subclinical episodes may be missed, and the conclusion that rejection does not occur simultaneously in the heart and kidney allograft may not be valid.

It has been argued that simultaneous, rather than staged, transplantation of cardiac and renal allografts is preferable because ischemic allograft injury increases expression of class I and class II histocompatibility complex antigens in experimental models. A longer ischemic time may render the renal parenchyma more immunogenic and may lead to poorer renal function with significantly reduced long-term survival. Although this was not observed in this series, we believe the staged approach (ie, implantation of the renal allograft is performed hours later as a separate surgical intervention) has several advantages. It allows for hemodynamic stabilization in the early postoperative period, particularly if hemodialysis was performed during cardiopulmonary bypass. The avoidance of right ventricular failure is of paramount importance in the eventual outcome of the renal allograft. Every attempt should be made to decrease the amount of inotropic support without compromising hemodynamics, in particular those agents that may be deleterious to the renal allograft (ie, α-adrenergic agents). For those reasons, the use of borderline or high-risk donors or those with a potential long ischemic cardiac allograft time are avoided. The prompt recovery of cardiac function is essential to the outcome of the renal allograft. Finally, the staged approach allows for correction of any coagulation abnormality that may be present as a result of chronic preoperative congestive heart failure. We believe that patients undergoing heart-kidney transplantation should be in optimal hemodynamic and hematologic condition before implantation of the renal allograft because the loss of the transplanted kidney would adversely affect their management and long-term results. In our experience a mean ischemic time of 23.3 hours was of no detriment to the renal allografts, and diuresis was observed soon after implantation. However, there is not enough accumulated experience with combined heart-kidney transplantation by any single transplant center to claim superiority of one approach over the other.

Finally, given the 1- and 2-year actuarial survival of % and %, respectively, of combined heart-kidney transplantation with an associated actuarial freedom of rejection of % at 1 year in a multi-institutional study, the indications for transplantation in patients with coexisting end-stage heart and kidney disease have been expanded. This is reinforced by the satisfactory long-term results and actuarial survival presented in this study. That is, potential heart transplant candidates with severe chronic renal dysfunction caused by a fixed and nonreversible parenchymal disease appear to be good candidates for combined heart-kidney transplantation. Although there are no established guidelines, it has been suggested that a glomerular filtration rate of less than mL/min, a serum creatinine level of more than mg/dL, or both, would be an indication for such combined organ transplantation. We use similar criteria for combined heart-kidney transplantation in our institution because these values seem to indicate the increased likelihood of postoperative renal failure, partly exacerbated by the nephrotoxic effect of immunosuppressive agents within a year after transplantation. However, because there is always some component of renal dysfunction in patients with severe congestive heart failure that may prompt a worse interpretation of the end-stage nature of the renal disease in the pretransplant period, a careful interpretation of these measured renal physiologic parameters is needed to avoid unnecessary transplantation of a renal allograft in a patient with potentially recoverable renal function. This approach is facilitated by the fact that our organ procurement
agencies allow for double-organ transplant listing from a single donor. Conversely, potential candidates for renal transplantation with coexisting end-stage heart disease not amenable to other cardiac operative interventions would be good candidates for combined heart-kidney transplantation.

It could be debated that this combined approach may not represent a rational or optimal use of the scarce donor resources available because 2 donor organs are allocated to a single individual with double-organ failure rather than 2 allografts being transplanted into 2 separate patients with single-organ failure. Although these issues are important, and as controversial as they may seem, the medical, ethical, and moral justification of allocation of donor organs goes beyond the scope of this article. Perhaps these questions can be partially answered by the satisfactory results, including quality of life, obtained in the patients described in this report.

In summary, on the basis of the good results obtained with combined heart-kidney transplantation, this approach has become an effective therapeutic option for a growing number of patients with coexisting end-stage heart and kidney disease. Intermediate and long-term results are similar to those of single-organ transplantation, with an observed low incidence of rejection when both allografts are from the same donor. Simultaneous rejection of both allografts is rare, and therefore rejection monitoring and surveillance should be carried out separately for each transplanted organ. The low rejection rate observed raises many immunologic questions and needs further clarification. The criteria for patient selection now seems well established, and our experience indicates that the staged approach for allograft implantation does not adversely affect the renal allograft and gives satisfactory long-term results. Finally, because of the limited experience of single centers with combined heart-kidney transplantation, multicenter studies with a larger patient population are needed to validate these results.

References