A 25 Year Review of Combined Cardiac and Renal Transplant Outcomes in Patients with End Stage Cardiac Failure on Renal Replacement Therapy. A Single Center Experience

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Abstract

Background: Combined heart and kidney transplantation has been shown to be a viable option for patients who have concurrent end stage cardiac and renal failure. However there is limited long term survival data that compares the outcomes of patients undergoing combined heart-kidney transplantation to patients undergoing solitary cardiac transplantation. There is also limited data on patients with end stage cardiac failure who are on concurrent renal replacement therapy prior to organ transplantation and their outcomes. This study reviews the short and long term outcomes of combined heart-kidney transplantation over a 25 year period in comparison to solitary cardiac transplantation in a majority of patients undergoing renal replacement therapy at time of transplant listing.

Methods and Results: In total there were 16 patients who underwent combined heart and kidney transplantation in the period between October 1990 and June 2014 (including heart and kidney re-transplantation) with 14 patients (87.5%) on renal replacement therapy at time of combined procedure. They were listed for combined heart and kidney transplantation as they fulfilled our institution’s criteria for irreversible end-stage heart and kidney failure. Retrospective review of patient data from the transplant database, patient case notes and post-mortem reports were carried out. Statistical analysis was then performed on key patient demographics alongside actuarial survival analysis, which were then graphically annotated. IRB approval was obtained and informed consent from patients was also obtained.

The mean (SD) recipient age was 42 (13) years and there were 3 females. Dilated cardiomyopathy was the most common primary cardiac pathology (50%) whilst ischemic nephrosclerosis (25%) and glomerulonephritis (25%) were the most common primary renal pathologies. Most patients experienced NYHA class IV symptoms (62.5%). The average wait time to transplantation at our institution was 12 months.

There was no operative mortality. The cumulative 1 year survival in the combined transplant group was 0.75 with 4 out of 16 mortalities within the first year (25%). In comparison the cumulative 1 year survival of the heart only transplant group was 0.86 with 116 mortalities within the first year over a 25 year period.

The incidence of cardiac rejection episodes in the study time was 9 out of 16 (56%) versus 3/16 (19%) who had renal rejection. In the study period there was 1 death out of 7 deaths due to dual graft failure.

Conclusions: Combined sequential cardiac and renal transplantation has good short- and long-term outcomes for patients with co-existing end stage cardiac and renal failure. At the ten year mark actuarial survival for combined heart and kidney transplantation is equivalent to cardiac transplantation alone.

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Introduction

Chronic kidney disease in the context of cardiac transplantation is a significant contributor to increased morbidity and mortality\cite{1,2}. In addition there is established evidence that between 30 - 40% of patients admitted to hospital with heart failure have concurrent renal impairment\cite{3,4} with significantly worse morbidity and mortality outcomes\cite{3,5-10}. Since the initial report of simultaneous heart-kidney transplantation in 1978, combined solid-organ transplantation has evolved into a viable option for patients with end stage cardiac and renal failure\cite{11-35}. This is especially important in the context of patients with end stage cardiac failure who are on renal replacement therapy, where solitary cardiac transplant alone may be contraindicated. We report our experience with 16 patients over a 25 year period 14 of whom were on concurrent renal replacement therapy which we believe is the longest retrospective review of patients to have undergone simultaneous combined heart and kidney transplantation and compared their outcomes to the outcomes of patients undergoing solitary heart transplantation at our institution.

Methods

A retrospective observational study was undertaken. During the period between October 1990 and June 2014, a total of 16 patients underwent combined heart and kidney transplantation at our institution. In the period between Feb 1984 and May 2014 a total of 866 patients underwent orthotopic heart transplantation at our institution.

A retrospective review of medical, surgical and intensive care records and the transplant database was completed on these 16 patients. The records were reviewed for patient demographics, co-morbidities, etiology of cardiac and renal failure, baseline cardiac and renal function, renal replacement requirement and duration of renal replacement prior to transplant, right heart study pre transplant, time on the transplant waiting list, peri-transplant acute and long term complications, rejection events, graft function and long term mortality outcomes. These results were documented and tabulated and patients numbered accordingly 1-16 in all tables (Table 1- 4). Data was summarized using means ± standard deviation for numeric variables and percents and counts for categorical variables. (Table 1,2)

Table 1: Patient Characteristics Pre Transplantation

| Patient | Age | Sex | Co-morbidities | Etiology of Renal Dysfunction | Kidney function Creatinine mmol/L | Duration of Renal Replacement Therapy Prior to Transplant or Post Transplantation Months | Etiology of Cardiac Dysfunction | EF | ECMO/LVAD prior to Tx | Right Heart Catheter - Pulmonary Artery pressure mmHg |
|---------|-----|-----|----------------|-----------------------------|---------------------------------|---------------------------------|-------------------------------|----|----------------------|-----------------------------------|
| 1       | 61  | M   | HPT, Dyslipidemia | Post Infection GN, Ischemic nephrosclerosis | 280 | 1 month HD post Tx | RF/Valvular CM+ IHD | 20% | IABP | 50 |
| 2       | 23  | F   | WilmsTumors, CKD, Aniridia | WAGR syndrome- Bilateral Wilms Tumors- Right nephrectomy Left partial nephrectomy: c1q GN in remaining kidney | Haemodialysis | 60 months pre transplant | Anthracycline induced cardiomyopathy. | 10% | IABP | 45 |
| 3       | 52  | M   | Hypertension, Dyslipidemia, Anemia, Secondary Hyperparathyroidism | Ischemic nephrosclerosis +/-cardiorenal syndrome | Haemodialysis | 96 months pre transplant | DCM | 15% | IABP | 40 |
| 4       | 27  | M   | DCM | Chronic Allograft nephropathy (Multiple Heart and Kidney Transplantation) | Continuous Ambulatory Peritoneal Dialysis | 12 months pre transplant | Allograft Vasculopathy (Multiple Heart and Kidney Transplantation) | 25% | Nil | 32 |
**Table 2:** Patient Characteristics Pre-Transplant

| Patient characteristics Pre-Transplant | Mean ± SD | Range | Percentage% |
|----------------------------------------|-----------|-------|-------------|
| Age at transplantation (y)             | 42.875 ± 13.0 | 16 - 61 |             |
| Male sex (13/16)                       |           |       | 81          |
| Dilated Cardiomyopathy (8/16)          |           |       | 50          |
| Ischemic Cardiomyopathy 3 (18.75%)     |           |       | 18.75       |
| NYHA class III (6/16)                  |           |       | 37.5        |
| NYHA class IV (10/16)                  |           |       | 62.5        |
| IABP/ECMO Peri-Transplant (5/16)       |           |       | 31.3        |
| LVEF (%)                               | 18.9 ± 5.7 |       |             |
| Mean Pulmonary Artery Pressure (mmHg)  | 36.7 ± 9.7 | 13 - 50 |             |

DCM: Dilated Cardiomyopathy. AF: Atrial Fibrillation. MI: Myocardial Infarct. CKD: Chronic Kidney Disease. CAPD: Continuous Ambulatory Peritoneal Dialysis. HD: Haemodialysis. MCG: Mesangiocapillary Glomerulonephritis. WAGR: Wilms Tumors, Aniridia, Genitourinary Abnormality, Mental Retardation syndrome. RF: Rheumatic Fever. ECMO: Extracorporeal Membrane Oxygenation. IABP: Intraaortic Balloon Pump. Tx: Transplant, Strep: Streptococcus.
The patient selection criteria include all patients with New York Heart Association class III and IV cardiac failure as per the International Society for Heart and Lung Transplant (ISHLT) indications for cardiac transplantation. The patients must have had concomitant renal failure with creatinine clearances of less than 30 mL/min and/or required renal replacement therapy at time of consideration for cardiac transplantation.

HLA typing was not done preoperatively on all patients and was omitted for the patients that did have them performed. The hearts were procured by the cardiac transplantation service at our institution, and the kidneys by the surgical team designated by the organ procurement coordinator. The heart transplant was performed first on table followed by kidney transplantation in all 16 cases.

Immunosuppressive therapy was documented and tabulated and changes to their regimen in the 25 year follow up period were documented. Endomyocardial biopsies were performed according to our institutions protocol or when cardiac rejection was suspected the grading was documented and tabulated (Table 3) as per the ISHLT classification. Only the most significant episode of rejection was documented. Renal rejection was confirmed with renal biopsies when clinically and biochemically suspected and rejection episodes tabulated (Table 3).

### Table 3: Acute Complications Post Transplant and Episodes of Rejection with Immunosuppressive Regimen

| Patient | Acute complications | Cardiac rejection | Renal Rejection | Immunosuppression Post Transplant | Current immunosuppression |
|---------|---------------------|------------------|----------------|----------------------------------|--------------------------|
| 1       | Sepsis from sternal wound infection- Resuting in Acute Renal failure | 3A rejection. Pulsed methylpred | Nil | Cyclosporine 100 mg bd, Mycophenolate 500 mg bd, Prednisone 10 mg daily | Cyclosporine 100 mg bd, Mycophenolate 500 mg bd, Prednisone 10 mg daily |
| 2       | Sepsis VRE, Pericardial Effusion | Nil | Yes | Cyclosporine 125 mg bd, Mycophenolate 1 g BD, Prednisone 10 mg | Tacrolimus 4 mg tds, Sirolimus 1 mg tds, Mycophenolate 1.5 g bd, Prednisone 25 mg daily |
| 3       | Cardiac Arrest- Resuscitated , ARF- HD, Leakage from bladder anastomosis, Herpes Simplex infection | 3A rejection. Pulsed methylpred | Nil | Cyclosporine 150 mgbd, Mycophenolate 1 g bd, Pred 15 mg bd | Tacrolimus 2 mg bd, Mycophenolate 1 g bd, Prednisone 15 mg bd |
| 4       | Stroke post transplant | Nil | Nil | Cyclosporine 100 mg bd, Azathioprine 150 mg daily, Prednisone 25 mg daily | Cyclosporin 100 mg bd, Prednisone 25 mg daily |
| 5       | Nil Significant | Nil | Nil | Cyclosporin 150 mg bd, Azathioprine 100 mg daily, Prednisone 12.5 mg daily | Cyclosporin 100 mg daily, Prednisone 25 mg daily |
| 6       | Cardiac Arrest off bypass. Resuscitated successfully | 1a rejection | Nil | Cyclosporin 250mg bd, Azathioprine 125 mg daily, Prednisone 25 mg daily | Cyclosporin 100 mg bd, Azathioprine 75 mg daily, Prednisone 10 mg daily |
| 7       | Nil Significant | Nil | Nil | Cyclosporin 25 mg Bd, Everolimus 0.5 mg mane, Mycophenolate 1 gbd, Prednisone 5 mg daily | Cyclosporin 25 mg Bd, Mycophenolate 1.5 g BD, Prednisolone 10 mg daily |
| 8       | VA ecmo post tx-Respiratory Failure- re intubated, sepsis (lung),ATN requiring CV-VHDF-HD post tx ,DIC, Ischemic hepatitis, GI bleeding | Nil | Nil | Cyclosporin 150 mg bd, Azathioprine 100 mg daily, Prednisone 12.5 mg daily | Cyclosporin 100/75, Mycophenolate 1.5 g BD, Prednisolone 10 mg daily |
| 9       | Nil Significant | 3A rejection. Methylprednisone | Nil | Cyclosporine 100 mg bd, Azathioprine 150 mg daily, Prednisone 10 mg | Cyclosporin 75/50, Mycophenolate 1 g bd, Pred 3 mg daily |
| 10      | Ureteric leak- HD post op | Mild 1a rejection | Nil | Cyclosporine 100 mg bd, Azathioprine 150 mg daily, Prednisone 10 mg | Cyclosporin 75/50, Mycophenolate 1 g bd, Pred 3 mg daily |
Cumulative survival outcomes were calculated with the actuarial method of estimation. The actuarial survival was calculated for the combined heart and kidney transplant group, the cardiac transplant only group with a subsequent comparison over a 25 year follow up period. These results were graphically analysed and compared.

**Results**

**Pre-transplant characteristics**

Patient demographic and clinical characteristics are indicated in Table 1. The mean and standard deviations of preoperative characteristics are indicated in Table 2. The mean age of the recipients was 42.9 with a range of 16 - 61. The majority of recipients were of Caucasian decent however there were 2 of Asian decent and 2 of Mediterranean decent. Thirteen of the recipients were male and three were female. 50% of the recipients had dilated cardiomyopathy as their primary cardiac pathology whilst ischemic nephrosclerosis or glomerulonephritis encompassed the majority of primary renal pathology at 50%. Five patients or 33% required ECMO or IABP prior to combined transplantation. The mean preoperative ejection fraction was 18.9 percent with a range of 10 - 30 percent. The mean pulmonary arterial pressure was 36.7 mmHg with a range of 13 - 50. Three patients were recipients of multiple organ transplantation and 1 of these patients was a recipient of sequential heart and kidney transplant followed by combined heart kidney transplant due to allograft failure.

**Postoperative outcomes**

There was no operative mortality in all 16 cases. The acute complications post transplant along with their initial immunosuppressant regimens are listed in Table 3. Their initial immunosuppressant regimen and their subsequent changes are also listed in Table 3.

One patient died within the first month of combined heart transplantation from multisystem organ dysfunction and sepsis. Sepsis from a respiratory source was the most common post operative complication with 31% of patients having a documented episode of significant respiratory sepsis. Two of these patients required re-intubation to support their respiratory function. Five patients or 31% required a period of renal replacement therapy post operatively. All except 1 patient was transitioned off renal replacement within the first 6 months post transplant.

There were 7 patients or 43% who had significant cardiac rejection with 2 patients experiencing mild cardiac rejection as per the ISHLT classification. Three or 19% of patients had documented renal rejection. Two of these patients did have a preceding significant episode cardiac rejection with only one patient having and isolated episode of renal rejection.

Renal graft function remained stable throughout the study period in 14 out of 16 patients or 87.5%. 11 out of 16 patients had stable cardiac function post combined transplant throughout the study period or 69% of the cohort.

Chronic allograft vasculopathy was the most common major complication in the study period with 25% of patients experiencing reduced cardiac function as a consequence.

The actuarial 1 year survival in the combined transplant group was 75% with 4 out of 16 dying within the first year (25%). In comparison the actuarial survival of the heart only transplant group was 86% accounting for 116 deaths within the first year of the 866 patients in this group over a 25 year period.

Actuarial survival at 5, 10, 15 and 25 years for the combined transplant group was 69%, 55%, 43.7% and 43.7% respectively. (Figure 1)
Combined Cardiac and Renal Transplant Outcomes

**Figure 1:** Cumulative Survival of Combined Heart Kidney Transplant over 25 years.

In comparison cumulative survival of the heart only transplant group at the 5, 10, 15, and 25 year mark was 76%, 59%, 45%, and 23% respectively. (Figure 2)

**Figure 2:** Cumulative Survival of Solitary Heart Transplant over 25 years.

The actuarial survival of the two groups over a 25 year period was then compared. (Figure 3) At the 10 year mark, actuarial survival for the combined group was comparable to the heart only transplant group with figures of 55% versus 59%.

**Figure 3:** Combined Heart Kidney Transplant Cumulative Survival Versus Solitary Heart Transplant Cumulative Survival over 25 years.

The main causes of death were sepsis resulting in multisystem organ failure, cardiac arrest and malignancy. There was a low incidence of dual graft failure as the primary cause of death. Most patients after the first year post combined procedure had a relatively good graft longevity and function.
The current study represents the longest single center experience of simultaneous combined heart kidney transplantation. It confirms and demonstrates that combined heart kidney transplantation has favourable short and long term outcomes for patients with end stage cardiac and renal failure especially when on renal replacement therapy at the time of transplantation which often is a contraindication in itself to solitary organ transplant.

The overwhelming majority of our patients were on renal replacement therapy at the time of their combined heart and kidney transplantation. Although there is conflicting analysis of registry data by Russo et al suggesting greater adverse outcomes of patients who underwent combined heart kidney transplantation whilst on renal replacement therapy in comparison to those not on renal replacement therapy with an EGFR of less than 30, our study showed markedly improved survival outcomes in 14 out of 16 of our patients or 87.5% of the cohort (Table 4). This emphasizes the superior outcomes for patients with concurrent end stage cardiac and renal failure requiring renal replacement therapy who undergoes combined cardiac and renal transplantation.

### Table 4: Long Term Graft Function and Complications Post Transplantation with Survival Outcomes and Cause of Mortality

| Patient | Renal Graft function- Creatinine mmol/l | Cardiac Graft function: Ejection fraction | Major Long term complications post transplantation | Minor Complications post transplantation | Graft survival | Patient survival | Cause of Death |
|---------|----------------------------------------|----------------------------------------|--------------------------------------------------|----------------------------------------|----------------|----------------|----------------|
| 1       | 100                                    | 50%                                    | 1. CMV gastritis/ esophagitis                      | Squamous Cell Skin Cancer               | Both Functional | Alive          | N/A            |
| 2       | Graft failure- Rejection Back on HD    | AMI-Cardiac graft failure              | CMV pneumonitis, Recurrent VRE urosepsis          | N/A                                    | Both grafts failed | Deceased | Cardiac Arrest |
| 3       | 159                                    | 42%                                    | Allograft vasculopathy                            | N/A                                    | Both Functional | Deceased | Cardiac Arrest |
| 4       | 125                                    | 50%                                    | Nil                                               | N/A                                    | Both Functional | Alive | N/A            |
| 5       | 120                                    | 60%                                    | 1. Recurrent infections: Staph, CMV, HSV, 2. Aortic Dilatation: Bentall’s CABG 04, 3. Allograft Vasculopathy | N/A                                    | Both Functional | Alive | N/A            |
| 6       | 130                                    | 60%                                    | Allograft vasculopathy                            | Squamous Cell Skin Cancer/ Bowens disease | Both Functional | Deceased | Allograft vasculopathy |
| 7       | 135                                    | 25%                                    | 1. Atrial Myxoma/ Atrial Thrombus, 2. Subdural Haemorrhage | N/A                                    | Both Functional | Alive | N/A            |
| 8       | 110                                    | 25%                                    | Nil                                               | N/A                                    | Cardiac Graft Failed | Deceased | Multisystem organ failure in ICU post Tx |
| 9       | 90                                     | 50%                                    | SCC- excision required. Mandibular excision       | HPT, Dyslipidemia, Gout, osteoporosis   | Both Functional | Alive | N/A            |
| 10      | 77                                     | 50%                                    | Malignancy - Non Lymphoproliferative/Disseminated adenocarcinoma CMV gastritis/ disseminated herpex zoster | N/A                                    | Both Functional | Deceased | Malignancy - Non Lymphoproliferative malignancy |
| 11      | 121                                    | 50%                                    | Nil                                               | Basal Cell Skin Cancer/ Bowens disease  | Both Functional | Alive | N/A            |
| 12      | 105                                    | 60%                                    | Nil                                               | N/A                                    | Both functional | Alive | N/A            |
| 13      | 80                                     | 35%                                    | P.E, Lymphoproliferative disorder((PTLD)         | N/A                                    | Both Functional | Deceased | Lymphoproliferative disorder |
| 14      | N/A                                    | N/A                                    | Sepsis                                           | N/A                                    | Both Functional | Deceased | Sepsis +multi-system organ failure |
| 15      | 220                                    | 28%                                    | Nil                                              | N/A                                    | Cardiac Graft Failed | Deceased | Graft failure |
| 16      | 135                                    | 50%                                    | Allograft Vasculopathy                            | Squamous Cell Skin Cancer               | Both Functional | Alive | N/A            |
Our study showed that kidney allograft function in the setting of combined heart kidney transplantation remained relatively intact with 15 out of 16 patients experiencing no renal graft failure. Simultaneous graft failure leading to death was observed in 1 patient in our study. This lower incidence of renal rejection was also reported in several other studies\([12,13,29]\). The overall rate of rejection was encouragingly low with the majority of patients experiencing more significant cardiac rejection episodes that responded to either intravenous pulse steroids with one patient requiring plasmapheresis. Why this immunological tolerance was observed in the donor kidney is potentially multi-factorial with more stringent monitoring for cardiac rejection and the previously proposed phenomena of immunogenic tolerance to the less antigenic organ in the context of combined transplantation\([29-36]\).

Most importantly given the 1,5,10, and 25 year actuarial survival of 75%, 69%, 55% and 43.7% respectively, combined heart kidney transplantation can be viewed as a viable option for patients with concurrent end stage cardiac and renal dysfunction\([37]\). Our study correlates closely with various other single center studies (Table 5) that have also demonstrated excellent short and long term survival outcomes of combined heart kidney transplantation over significant time periods.

### Table 5: Survival Rate and Duration of Follow Up of Combined Heart Kidney Transplantation in a Single Center.

| Studies          | 1 year survival % | 5 year survival % | Number of Patients | Duration of Follow Up |
|------------------|-------------------|-------------------|--------------------|----------------------|
| Raichlin et al\([15]\) | 83                | 83                | 12                 | 10 years             |
| Luckraz et al\([19]\) | 77                | 60                | 13                 | 15 years             |
| Vermes et al\([16]\) | 66                | 55                | 12                 | 10 years             |
| Trachiotis et al\([22]\) | 87               | 87                | 8                  | 8 years              |
| Leesera et al\([17]\) | 77                | 60                | 13                 | 10 years             |
| Ruzza et al\([35]\) | 90                | 70                | 30                 | Ruzza et al 35       |

The challenge to combined heart kidney transplantation is the rationality and ethical dilemma surrounding combined organ transplantation given the limitations and constraints surrounding donor organ availability. In most cases multiple organs from either a single or multiple donors will be transplanted into a single recipient, posing a significant burden on the already limited resources of the state-wide and national transplant service. The overall waitlist times for combined heart kidney transplantation with a mean of 12.1 months in our study offers further emphasizes that this is a viable option with acceptable waiting times for patients with dual heart and kidney failure.

### Conclusion

In conclusion, the results of this study further emphasizes that combined heart kidney transplantation produces good short and long term outcomes for patients with end stage heart and kidney failure and especially patients with end stage heart failure on renal replacement therapy. These favourable survival outcomes and lower rates of organ rejection with combined transplantation has now been reproduced consistently from multiple international centers with different selection criteria, making combined heart kidney transplantation a viable and effective therapeutic option for patients with end stage cardiac and renal failure who would previously not have qualified for solitary organ transplantation.

### Conflicts of Interest: No disclosures in the submission of this work.

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