JOURNAL READING: COMBINED HEART-KIDNEY TRANSPLANTATION: THE UNIVERSITY OF WISCONSIN EXPERIENCE

Presenter: Intern

Background: Combined cardiac and renal transplantation, HKTx

- The incidence of HKTx has been increasing with time
- Populations of patients with end-stage cardiac and renal disease are growing
- According to the records of the United Network for Organ Sharing (UNOS) from 2006.11
  - 448 HKTxs were performed
  - 1.2% of all transplanted hearts
- Analysis of outcomes compared to single-organ recipients is needed

Methods

- A retrospective review of prospectively collected data for HKTx patients
- Sources: Institutional and UNOS databases and individual charts
- Study cohorts: since 1987
  - HKTx (n=19)
  - Heart alone transplant, OHTx (n=515)
  - Kidney alone transplant, KTx (n=3188)
  - Kidney-alone after heart-alone transplant, KTx p OHTx (n=8)

Methods: Cohorts

- HKTx (n=19)
  - Prior kidney transplant: 1 in 19 patients
  - All recipients had end-stage cardiac disease and renal insufficiency or failure
  - OHTx (n=515)
  - 29 patients died peri-operatively
  - 4 had incomplete medical records
  - 482 patients constituted the final cohort

Methods: Cohorts

- KTx (n=3188)
  - Cadaveric donor: 2,091 patients
  - Living donor: 1,097 patients
- KTx p OHTx (n=8)
  - Cadaveric donor: 4 patients
  - Living donor: 4 patients
Methods: Causes of Organ Failure

Table 2. Organ Failure Biology Data

<table>
<thead>
<tr>
<th></th>
<th>Heart</th>
<th>Kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Hypoperfusion/heart disease</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Primary disease</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Alcoholic</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Hematologic</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

Methods: Detection and Management of Graft Rejection

Endomyocardial biopsy rejection screening protocol
- Performed during the 1st year post-transplant
- Checked up yearly or according to symptoms

Indication for treatment of rejection
- ISHLT grade >2 (before)
- ISHLT grade >3A or altered hemodynamics
- Because most patients in this study were transplanted prior to this change, heart graft rejection in this study is defined as ISHLT Grade 2

Methods: Detection and Management of Graft Rejection

Rejection of ISHLT > Grade 2
- For transplants <3 months old
- For transplants >3 months old and stable hemodynamics

Methylprednisolone 250 mg/day for 3 days
Prednisone 50 mg/day for 3 days

Methods: Definition of Coronary Allograft Vasculopathy

Yearly cardiac catheterization
- Endomyocardial biopsy
- Hemodynamic measurement
- Coronary angiography
- Additional angiographic studies
- According to patients symptoms at the discretion of transplant cardiologists and/or cardiothoracic transplant surgeons

A patient was said to have CAV if that diagnosis appeared in the cardiologist’s procedure report

Methods: Immunosuppression

Triple-drug therapy is standard
- In OHTx, new practice suggested steroid tapering to zero in 18 months post-transplant
- In HKTx, patients remain on steroids, eventually tapering to a 5 mg/day maintenance

Table 3. Immunosuppression Regimens

<table>
<thead>
<tr>
<th>Immunosuppressive Treatment</th>
<th>OHTx</th>
<th>HKTx</th>
<th>KTx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>Steroid only</td>
<td>Steroid only</td>
<td>Steroid only</td>
</tr>
<tr>
<td>Prednisone maintenance</td>
<td>0-5 mg/day</td>
<td>0-5 mg/day</td>
<td>Variable</td>
</tr>
<tr>
<td>Anti-rejection</td>
<td>AzA or MMF</td>
<td>AzA or MMF</td>
<td>AzA or MMF</td>
</tr>
<tr>
<td>Calcineurin inhibitor (CIL)</td>
<td>CsA or tacrolimus</td>
<td>CsA or tacrolimus</td>
<td>CsA or tacrolimus</td>
</tr>
<tr>
<td>CsA Level</td>
<td>Immediate</td>
<td>Immediate</td>
<td>Immediate</td>
</tr>
<tr>
<td>CsA maintenance</td>
<td>CsA or tacrolimus</td>
<td>CsA or tacrolimus</td>
<td>CsA or tacrolimus</td>
</tr>
<tr>
<td>CsA + MMF</td>
<td>CsA + MMF</td>
<td>CsA + MMF</td>
<td>CsA + MMF</td>
</tr>
<tr>
<td>CsA + CsA</td>
<td>CsA + CsA</td>
<td>CsA + CsA</td>
<td>CsA + CsA</td>
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</tbody>
</table>
Results: Donor Characteristics
- Average age: no statistically difference (P < 0.01)
  - HKTx donors: 24 years, OHTx donors: 30.2 years
- Coronary angiography (> 40 y/o, n=2):
  - Mild coronary artery disease (n=2)
  - Mild left ventricular hypokinesis (n=1)
- Echocardiography (n=4):
  - Mild LV hypokinesis (n=1)
  - Normal ventricular function (n=3)
  - Mild mitral regurgitation (n=2)

Results: Donor Characteristics
- 13 donors received dopamine at an average dose of 9 g/kg/min
- 2 donors also concomitantly received phenylephrine
- 1 received phenylephrine and norepinephrine
- 1 received norepinephrine alone
- No donor received inotropic agents

Results: HKTx Clinical Course
- Average cold ischemic time
  - Heart: 3.1 ± 1.0 hrs, Kidney: 18 ± 7.2 hrs
- In-hospital HKTx death (n=1)
- Average length of in hospital: 36 days
- Dialysis-dependent before HKTx (n=8)
- Transient renal replacement therapy (n=8)
  - 4 of 8 were Dialysis-dependent before HKTx
- Delayed kidney graft function (n=2)

Results: Complications
- Intracranial hemorrhage (n=1)
- Ogilvie’s syndrome (n=1)
- Respiratory failure (n=1)
- Recurrent pericardial effusion (n=1)
- Multiple infectious problem (n=2)
  - Prolonged post-transplant hospital days (n=2)
  - Expired before discharge (n=1)
- Mortality in follow-up (n=5)
  - Sepsis (n=2), Cardiac graft amyloidosis (n=1), Squamous cell lung cancer (n=1), Unknown (n=1)

Results: Patient Survival
- KTx > OHTx
- HKTx: No difference

Results: Graft Survival
- Heart Graft Survival: No difference
- Kidney Graft Survival: No difference
Results: Rejection

- Rejection-free survival time for kidney graft significantly prolonged in HKTx than KTx.

- Rejection-free survival time for heart graft significantly prolonged in HKTx than OHTx.

Discussion

- HKTx is an important modality for treating patients with end-stage cardiac and renal disease.
- Rising incidence of HKTx was noted in recent years:
  - An increase in recipient population
  - Increased willingness of the transplant community to perform the procedure
  - Increasing donor organ availability
- Scarcity of this resource demands critical analysis of all transplant outcomes.

Advantages of the Study

- The largest single-institution review of the scarce patient population of HKTx.
- Analyze rejection as a temporally defined continuous variable (rejection-free survival, RFS) to minimize survivor bias.
- This is the first study to demonstrate increased RFS for both heart and kidney grafts after HKTx compared with heart or kidney transplant alone.

Points of Other Studies

- No significant differences in patient and heart graft survival and RFS for HKTx vs OHTx.
- No difference in survival, but significant less rejection incidence at 6 months and 1 year (HKTx< OHTx).
- By Vermees et al.

- No difference in survival, but significantly less cardiac rejection in the HKTx group.
- By Vermees et al.

Points of Other Studies

- Narula et al compare survival between 82 HKTx and 14,340 OHTx patients from UNOS.
  - No difference in survival (mean follow-up 2.14 ± 2.04 years).
  - Decreased frequency of heart rejection in HKTx recipients.

Results: Coronary Allograft Vasculopathy (CAV)

- Time to develop CAV:
  - No difference.

Overall incidence of CAV:

- Significantly lower for HKTx patients.
Discussion

- No difference in patient/heart graft survival between HKTx and OHTx, KTx or KTx p OHTx patients
- In addition, kidney graft survival did not differ for HKTx vs KTx (either cadaveric or living donor KTx)
- Both cardiac and renal graft RFS was prolonged for HKTx recipients compared with recipients of single organs
  - Overall kidney graft survival at a mean follow-up of 4.9 ± 3.6 years is 95%

Discussion of Rejection Free Survival

- Increased RFS was noted in KTx p OHTx compared with KTx
  - May be due to transplantation into an already immunosuppressed patient
- No changes in RFS in cardiac allograft was noted with the addition of a renal graft
  - It is past the period of frequent and expected cardiac rejection
- Addition of a kidney graft in an established OHTx patient does not cause an increase in cardiac rejection activity

Reasons for Increased RFS for Both Heart and Kidney Grafts after HKTx

- Shorter renal cold ischemic times
- The greater antigenic load conferred by a kidney induces some tolerance that protects the heart graft
- Specialized immune cells are transferred with a renal graft
- A statistically significant difference in age between HKTx and OHTx donors in the study
- An imbalance in immunosuppression between the groups
- Antibody-mediated induction therapy

CAV in HKTx

- Groetzner et al
  - HKTx that received tacrolimus exclusively
  - A 0% incidence of CAV among HKTx recipients in 4.7 ± 2.0 years of follow-up.
- Pinderski et al
  - Retrospectively compared 348 OHTx and 8 HKTx patients
  - A 32% (OHTx) and 0% (HKTx) incidence of CAV by 3 years of follow-up
- In this study, 2 of 16 (12.5%) HKTx patients were diagnosed with CAV in 4.9 ± 3.6 years of follow-up

CAV in HKTx

- Analyzed as a categoric variable, HKTx patients had significantly less CAV compared with OHTx patients
- We did not perform sub-group analyses according to calcineurin-inhibiting agent
- Not every patient underwent catheterization every year so the exact incidence of CAV was not delineated in this study
Conclusions

- HKTx is associated with prolonged rejection-free survival times for both organs; however, this does not yield improved overall graft or patient outcomes compared with OHTx and KTx cohorts.

Further directions

- Assessing outcomes after HKTx is the first step toward validating allocation of multiple organs to single recipients.
- Developing algorithms to identify and discern between patients who benefit from this approach and those who can do without (generally without a simultaneous kidney) will aid future allocation decisions.
- Clearly, patients who are dialysis-dependent at the time of heart transplant should undergo HKTx.

Further directions

- However, this profile applied to only 40% of patients in our series and 48% of HKTx patients reported to UNOS during the last 12 years.
- It is less clear if the other 60% (in our study) and 52% (reported to UNOS), respectively, would have required a kidney transplant in the long term.

Further directions

- A recent study suggested that a glomerular filtration rate of 60 ml/min might be a threshold predicting future need, but there is no consensus on this issue.
- Other risk factors for progression of kidney disease after heart transplantation, such as diabetes, must also be considered.

Further directions

- At our institution, nephrologists make the HKTx vs OHTx decision for patients not yet on dialysis on an individual basis, without a set protocol.
- Most HKTx patients who were initially referred for OHTx had a progressive decline of renal function, or initiated dialysis while on the wait-list.

In Patients Received KTx after Previous Heart Transplantation

- 3 patients could probably not have been accurately predicted to need a kidney at a later time, as significant post-OHTx hypotension likely contributed greatly to their eventual renal failure.
- The remaining 5 of 8 patients who went on to need a kidney could be considered the author's misses.
The goal remains to distinguish accurately which patients with chronic kidney disease evaluated for OHTx need to undergo HKTx. Accomplishing this goal will aid allocation strategies, maximize donor organ utilization, minimize rejection morbidity, and streamline transplantation processes.

Thank you for your attention!

**ISHLT Rejection Grading**
- No evidence of rejection; ISHLT Grade 0
- Focal perivascular infiltrate without necrosis; ISHLT Grade 1A
- Focal interstitial infiltrate without necrosis; ISHLT Grade 1A
- Diffuse but sparse interstitial infiltrate without necrosis; ISHLT Grade 1B

**ISHLT Rejection Grading**
- Single focus of infiltrate with associated myocyte damage; ISHLT Grade 2
- Two to three foci of infiltrates with associated myocyte damage; ISHLT Grade 2-3A
- Multifocal interstitial infiltrates with associated myocyte damage; ISHLT Grade 3A
- Diffuse inflammatory infiltrates with associated myocyte damage; ISHLT Grade 3B
- Diffuse polymorphous infiltrate with myocyte necrosis, edema, hemorrhage, and/or vasculitis; ISHLT Grade 4