Vascular Remodelling in Pancreas Transplantation

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Consultant HPB/Transplant Surgeon
The Freeman Hospital Newcastle
President Elect EPITA
SPK Pancreas Graft Function

USA Primary DD Pancreas Transplants, 1/1/1966 – 12/31/2015

% 100

Months Posttransplant

0 24 48 72 96 120 144 168 192 216 240

1966-87
1988-93
1994-98
1999-03
2004-08
2009-15
SPK Kidney Graft Function

USA Primary DD Pancreas Transplants, 1/1/1966 – 12/31/2015

Months Posttransplant

%
PTA Pancreas Graft Function

USA Primary DD Pancreas Transplants, 1/1/1966 – 12/31/2014

% vs Months Posttransplant

- 1966-87
- 1988-93
- 1994-98
- 1999-03
- 2004-08
- 2009-15
# Pancreas Graft Function

**USA DD Pancreas Transplants, 1/1/2003 – 12/31/2012**

<table>
<thead>
<tr>
<th></th>
<th>SPK (8,345)</th>
<th>PAK (1,869)</th>
<th>PTA (884)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary only</td>
<td>All Tx</td>
<td>Primary only</td>
</tr>
<tr>
<td>1-Year</td>
<td>86.2%</td>
<td>88.0%</td>
<td>78.6%</td>
</tr>
<tr>
<td>3-Year</td>
<td>79.7%</td>
<td>81.4%</td>
<td>66.8%</td>
</tr>
<tr>
<td>5-Year</td>
<td>73.0%</td>
<td>77.5%</td>
<td>58.1%</td>
</tr>
</tbody>
</table>
Anti-T-Cell Induction

USA DD Primary Pancreas Transplants 1/1/1988 – 12/31/2015

Graph showing the percentage of anti-T-cell induction from 1988 to 2015 for different transplant types: PAK, PTA, and SPK.
HLA A, B, DR Mismatching
USA Primary DD Pancreas Transplants 1/1/1988 – 12/31/2015

% of 5 or 6 HLA Mismatch

Transplant Year


PAK
PTA
SPK
cPRA levels > 20%

USA DD Primary Pancreas Transplants 1/1/2004 – 12/31/2015
1-Yr Immunological Graft Loss

USA DD Primary Pancreas Transplants, 10/1/1988 – 12/31/2003
Causes of Pancreas Graft Failure
3 - <12 Month Posttransplant

USA Primary DD Pancreas Transplants 1/1/2010 – 12/31/2015

Pancreas Graft Failure Cause

%
Causes of Pancreas Graft Failure
≥ 1 - 5 Years Posttransplant

USA Primary DD Pancreas Transplants 1/1/2000 – 12/31/2015

Pancreas Graft Failure Cause
SPK Pancreas Graft Loss due to Chronic Rejection

USA DD TS Primary Pancreas Transplants, 1/1/1988 – 12/31/1999
CHRONIC REJECTION: THE NEXT MAJOR CHALLENGE FOR PANCREAS TRANSPLANT RECIPIENTS

Abhinav Humar, Khalid Khwaja, Thiagarajan Ramcharan, Massimo Asolati, Raja Kandaswamy, Rainer W. G. Grueßner, David E. R. Sutherland, and Angelika C. Grueßner

Objective. With newer immunosuppressive agents, acute rejection and graft loss resulting from acute rejection have become less common for pancreas transplant recipients. As long-term graft survival rates have improved, an increasing number of grafts are being lost to chronic rejection (CR). We studied the increased after all types of abdominal and thoracic transplants. A better understanding of donor and recipient risk factors, coupled with improvements in preservation and surgical techniques, also helped decrease the incidence of graft loss to technical complications.

As a result, an increasing number of pancreas grafts are

<table>
<thead>
<tr>
<th>Table 1. Causes of graft loss</th>
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<tr>
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<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Still functioning</td>
</tr>
<tr>
<td>Technical failure</td>
</tr>
<tr>
<td>Chronic rejection</td>
</tr>
<tr>
<td>Acute rejection</td>
</tr>
<tr>
<td>Death with function</td>
</tr>
<tr>
<td>Primary nonfunction</td>
</tr>
<tr>
<td>Other/unknown</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

PAK, pancreas after kidney transplant; PTA, pancreas transplant alone; SPK, simultaneous pancreas-kidney transplant.
## Table 2. Multivariate analysis of risk factors for CR after pancreas transplants

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>RR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute rejection</td>
<td>4.41</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Transplant category</td>
<td>3.02</td>
<td>0.002</td>
</tr>
<tr>
<td>CMV infection</td>
<td>2.41</td>
<td>0.001</td>
</tr>
<tr>
<td>Retransplant</td>
<td>2.27</td>
<td>0.004</td>
</tr>
<tr>
<td>PRA &gt; 20</td>
<td>1.73</td>
<td>0.10</td>
</tr>
<tr>
<td>Recipient age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \leq 45 ) (vs. &gt;45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of mismatches at A locus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2 (vs. 0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of mismatches at B locus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2 (vs. 0)</td>
<td>1.68</td>
<td>0.04</td>
</tr>
<tr>
<td>Number of mismatches at DR locus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 or 2 (vs. 0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunosuppression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMF (vs. other)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sirolimus (vs. other)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CMV, cytomegalovirus; PAK, pancreas after kidney transplant; PTA, pancreas transplant alone; SPK, simultaneous pancreas-kidney transplant; PRA, panel-reactive antibody; CR, chronic rejection; NS, not significant; RR, relative risk.
Distinct Histologic Patterns of Acute, Prolonged, and Chronic Rejection in Vascularized Rat Pancreas Allografts

BIRTE STEINIGER, MD, and JÜRGEN KLEMPNAUER, MD

From the Centre of Anatomy and Department of Abdominal and Transplantation Surgery, Medical School, Hannover, Federal Republic of Germany

In a model of pancreas whole organ transplantation in streptozotocin diabetic rats distinct histologic patterns of acute, prolonged and chronic rejection were defined by light microscopy. Allotransplantation between major f morphological differences were apparent. A unique feature was the preservation of normal acinar morphology. The impact of surgical techniques with preserved and suppressed exocrine secretion on graft histology was sequentially assessed in pancreas isograft recipients. MHC incompatibility was associated with acute rejection, non-MHC disparity with prolonged rejection and RT1.C mismatch with chronic rejection. (Am J Pathol 1986, 124:253-262)
Longitudinal Histopathologic Assessment of Rejection After Bladder-draed Canine Pancreas Allograft Transplantation


From the Pancreas Transplant Research Grc
Department of Surgery,† University of Sydney Hospital, Sydney, Australia

lems of graft pancreatitis and vascular thrombosis. Fur-
thermore serum and urine markers of rejection either oc-
cur late or are unreliable and are prone to misinterpre-
tation because of the reluctance of clinicians to per-

Figure 6. Summary of vascular changes, un-
modified by immunosuppression, seen after cani
e pancrease allograft transplantation (R,
rejection).
Morphologic features of chronic rejection in kidney and less commonly transplanted organs


Abstract: Chronic rejection is characterized by morphological evidence of destruction of the transplanted organ. The injury to the organ is associated with collagenization of variable degree. The destruction and fibrosis of the organ is probably the result of 1) direct alloimmune cytotoxic rejection (rejection) of the organ tissue, and 2) to fibroproliferative endarteritis (i.e., periglomerular fibrosis). The morphological feature of chronic fibroproliferative endarteritis, which is characterized by smooth muscle cell proliferation and intimal fibrosis, is a prominent feature of chronic rejection.

Richard K. Sibley
Department of Surgical Pathology, Stanford University Medical Center, Stanford, California, U.S.A.
Histological Grading of Chronic Pancreas Allograft Rejection/Graft Sclerosis

John C. Papadimitriou\textsuperscript{a, x}, Cinthia B. Drachenberg\textsuperscript{a}, David K. Klassen\textsuperscript{b}, Lillian Gaber\textsuperscript{c}, Lorraine C. Racusen\textsuperscript{d}, Ludek Voska\textsuperscript{e}, Charles B. Cangro\textsuperscript{b}, Emilio Ramos\textsuperscript{b}, Ravinder Wall\textsuperscript{b}, Matthew R. Weir\textsuperscript{b} and Stephen T. Bartlett\textsuperscript{f}

Introduction

Biopsy-proven chronic rejection (CR) is the largest single cause of late pancreas allograft loss (1–3). The clinical presentation of CR is nonspecific, with loss of glycemic control being the main feature. Hyperglycemia may develop progressively or may be unmasked by infection or other physiologic stresses (1). However, the clinical usefulness of this feature is limited since with the development of hyperglycemia due to chronic rejection, the beta cell function is in general already irretrievably lost (1). The diagnostic specificity of hyperglycemia is also
Figure 2: Grade I – Mild chronic rejection/graft sclerosis.
Expansion of fibrous septa (<30% of core surface). The lobules show peripheral erosion and fragmentation, but the central areas are intact.
Figure 6: Acute and chronic rejection grades in serial biopsies from a PTA recipient who lost graft function 34 months after transplantation. Repeated episodes of acute rejection (including late rejections) and several instances of acute rejection grade IV occurred over time. Chronic rejection/graft sclerosis was initially non-existent but gradually progressed, leading to loss of graft function.
Vanishing Pancreatic Grafts

Christopher Pivetti¹, In Chul Hong¹, Chang H. Yoo¹, Sun Lee¹, Kenny Kim¹, Gregory Emmanuel¹, Jason Kim¹, Romy Chung¹, Slawomir Niewiadomski², Paul Wolf³, and R. F. Gittes⁴

From the ¹San Diego Microsurgical Institute, ²Scripps Mercy Hospital, ³University of California San Diego Medical Center, ⁴Scripps Clinic.

Comparison of pancreaticoduodenal transplants (PDT) and duct-ligated pancreas transplant (DLPT) were performed using syngeneic and allogeneic studies in rats. Both DLPT and PDT allogeneic grafts showed mild rejection. DLPT groups showed disorganized pathology and acini replaced by fat. Eventually, massive fibrosis was seen in the Islets of Langerhans, as well as rejection cellular infiltrates. In both PDT groups, normal histology was observed in the same period. Thus the effect of duct occlusion is highly detrimental for the grafts.

Key Words: Pancreaticoduodenal transplants, duct-ligated pancreas transplants

MATERIALS AND METHODS

Lewis (LW) and Sprague Dawley (SD) rats, weighing 250g to 300g of mixed sex were employed for syngeneic and allogeneic studies, respectively. Though SD strains of rats were inbred at the San Diego Microsurgical Institute for over 15 generations, transplantation of solid organs (heart or pancreas) between SD strains still shows mild to moderate rejection phenomena. Grafts between inbred LW strains shows absence of rejection...
Vascular remodelling

- Physiological process triggered by a number of insults
- Differs from pathological stenotic disease
  - Rejection
  - donor specific antibodies
- Incidental observation of pancreatic graft vessel narrowing necessitated further investigation after a change in practice on post-op imaging
Renal Arterial Late
## Results

- 8 patients
- 12 month period
- Standard immunosuppression
  - Alemtuzmab Tacrolimus, MM
- Surgical technique-Systemic

### Procedure

- PAK: 25%
- SPK: 75%

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statistic</th>
</tr>
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<tbody>
<tr>
<td>Sex - M:F</td>
<td>7:1</td>
</tr>
<tr>
<td>Recipient age</td>
<td>Median 43 (32-55)</td>
</tr>
<tr>
<td>Donor age</td>
<td>28 (9-51)</td>
</tr>
<tr>
<td>CIT</td>
<td>9.8 (7.4-13.5)</td>
</tr>
<tr>
<td>Drainage – Enteric:Bladder</td>
<td>6:2</td>
</tr>
</tbody>
</table>
Aims/methods

- Examine changes in axial/coronal diameters of the arterial conduit, external iliac artery (EIA), internal iliac artery (IIA), superior mesenteric artery (SMA), splenic artery (SA) and renal arteries
- Retrospective CT analysis
  - Measurements were made by experienced radiologists
Imaging timescales

• In 2012 CT angiography became routine for pancreas transplants in the early (<5 days) and late (<6 months) post-transplant period

- **Transplant**
- **1st scan**
  - Median 4 d
  - Range 1-5
- **2nd scan**
  - Median 88 d
  - Range 33-162
## Mean Δ luminal diameter (mm)

<table>
<thead>
<tr>
<th></th>
<th>Renal artery</th>
<th>SMA</th>
<th>Splenic</th>
<th>EIA</th>
<th>IIA</th>
<th>Conduit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median % Δ (range)</td>
<td>0 (40-70.4)</td>
<td>-50 (50-86.7)</td>
<td>-60 (0-80)</td>
<td>-70.8 (0-80)</td>
<td>-57.8 (50-80)</td>
<td>-30.7 (0-77.8)</td>
</tr>
<tr>
<td>P value</td>
<td>n/a</td>
<td>&lt;0.01</td>
<td>0.012</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*Graph shows the mean Δ luminal diameter for different arteries with early and late stages.*

*Table shows the median % Δ with corresponding ranges and their associated P values.*
Morbidity

- Acute rejection (n=1)
  - Resolved with steroids
  - Arterial branch thrombosis (n=2)
  - Anticoagulated
- Collection (n=2)
- Pancreatitis (n=1)
Follow up

- All grafts functioning @ median follow up 15 months (range 10-21)
- All patients insulin independent
- 3 patients developed de novo DSA
- Occurs independently of DSA
- No CMV infections
Summary

• Luminal narrowing of large pancreatic allograft vessels
  ▫ No corresponding changes in renal arteries
• No apparent impact on short term graft function/survival
• ? Aetiology

<table>
<thead>
<tr>
<th>Physiological remodelling</th>
<th>Pathological disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Compensatory due to reduced demand</td>
<td>• Stenotic vasculopathy</td>
</tr>
<tr>
<td></td>
<td>• Immunological/rejection related</td>
</tr>
</tbody>
</table>
Transplant vasculopathy

**Increased medial tone**
- secondary to reduced vasodilator production or response or increased vasoconstrictor activity
- ↑ wall shear stress

**Adventitial fibrosis**
- limit the ability of the perivascular ECM to positively remodel and will indirectly lead to luminal compromise

**Intimal hyperplasia**
- recruitment of inflammatory cells and SMLCs and elaboration of ECM
Clinical implications

- Risk of thrombosis
- Graft survival
- Therapeutic Modulation-anti-angiogenesis
- PDGF, BMP4, A20, uric acid