Disclosures

- Off Label use: Optiflow
- Consultant/Advisory Board: Bioconnect, Pervasis, WL Gore, NanoVasc, Proteon
- Grant/Research Support: Bioconnect, WL Gore, Proteon
- Clinical Trial Support: NIH, Pervasis, Proteon, Ark, WL Gore

Our Current Understanding of Vascular Access Biology and Future Directions: Opportunities and Challenges for a Young Specialty
Gerald Beathard State of the Art Lecture ASDIN 2011

Prabir Roy-Chaudhury MD, PhD, FACP
University of Cincinnati and Cincinnati VAMC

Outline

- Pathology and pathogenesis of dialysis access stenosis
- Interactions between hemodynamics and vascular biology (central to dialysis vascular access dysfunction)
- Novel therapies that target both hemodynamics and vascular biology
- Message for the future!!

Houston; we have a problem!!

Primary Patency Results

- CABG (LIMA) 90% @ 10 years
- CABG (SV) 50% @ 10 years
- Aorto-bifemoral bypass 90% @ 5 years
- BK Femoro-popliteal bypass 33% @ 5 years
- AVG Surgery 23% @ 1 year
- AVF Surgery 40% @ 1 year

A message for the present!!

- Current modalities and therapies for dialysis vascular access are not very effective
- Lack of understanding about the actual mechanisms involved in dialysis access stenosis

Don't worry, I'll find a good site soon!!
**Clinical presentation of dialysis vascular access**

- Perianastomotic stenosis
- AVF non-maturation and late AVF stenoses
- Stenosis at the graft-vein anastomosis
- Graft thrombosis

**Venous neointimal hyperplasia is made up of myofibroblasts**

- Migrated in from the media and perhaps the adventitia
- Response to endothelial and smooth muscle cell injury

**Vascular Injury in the Setting of Hemodialysis Vascular Access Dysfunction**

- Hemodynamics
- PTFE Graft
- Dialysis Needle
- Surgical Injury
- Poor Vascular Biology
- Angioplasty

**Angioplasty: the Good, the Bad and the Ugly**

Angioplasty: Outward remodeling due to intima-media rupture

- Restenosis due to neointimal hyperplasia

Angioplasty: Decreased cumulative AVF survival in patients requiring angioplasty for AVF maturation

- No interventions
- 1 intervention
- 2 interventions

(Adapted from Peter Ballyk)

**Dialysis access stenosis is a balance between vascular remodeling and neointimal hyperplasia**

- Significant Neointimal Hyperplasia + Expansive Remodeling
- Minimal Neointimal Hyperplasia + Negative Remodeling

(Mature AVF)

(AVF maturation failure)

(Adapted from Mike Conte)
In an ideal world!!!

**Increase in Flow**
- Creation of dialysis access
- Increased Flow
- Increased endothelial production of NO
- Inhibits neointimal hyperplasia
- Successful use of AV fistula/graft
- Expansive or outward remodeling

**Vascular Response to Flow**
- Hemodynamic and vascular biology interactions
  - **Upstream Hemodynamics (Flow)**
  - **AVF/AVG Failure**
  - **AVF/AVG Creation**
  - **Downstream Vascular Biology (Response to Flow)**

Flow patterns and shear stress influence endothelial function

**Hemodynamics 101**
- Non laminar flow with oscillatory shear (LOW)
- Endothelial activation
- Increased Oxidative Stress
- Inflammatory gene profile (VCAM-1)
- Endothelial quiescence
- Minimal Oxidative Stress
- Non-Inflammatory gene profile (Nitric oxide)

**Surgical configuration influences shear stress profiles**
- **Curved**
- **Straight**

Blood flow is greater in the curved configuration

<table>
<thead>
<tr>
<th>Time Point (Days)</th>
<th>Flow Rate (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5000</td>
</tr>
<tr>
<td>5</td>
<td>4000</td>
</tr>
<tr>
<td>10</td>
<td>3000</td>
</tr>
<tr>
<td>15</td>
<td>2000</td>
</tr>
<tr>
<td>20</td>
<td>1000</td>
</tr>
<tr>
<td>25</td>
<td>500</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
</tr>
</tbody>
</table>

**p < 0.05**

Diameter is greater in the curved configuration

<table>
<thead>
<tr>
<th>Time Point (Days)</th>
<th>Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
</tr>
</tbody>
</table>

**p < 0.05**

Anatomy, Shear and Stenosis!

**Optimize** surgical configuration for AVFs and PTFE grafts using surgical devices

↓

**Ideal** flow patterns and shear stress profile in AVFs and PTFE grafts

↓

Reduce AVF and PTFE graft stenosis

---

**Intrinsic Endothelial (dys)function**

- Hemodynamic forces can influence endothelial response = **YES**
- Why do dialysis vascular access procedures have such poor survival?
- Focus on the intrinsic function or dysfunction the baseline endothelial cell and how this influences its response to shear stress alterations??

---

**ESRD and CKD are states of massive endothelial dysfunction!!**

- Uremia
- Oxidative stress
- Inflammation

**Reduction in flow mediated dilation** (marker of endothelial function)

- Kopel et al. F-P0038, ASN 2009

**Uremic mice have increased AV fistula stenosis**

- Choi et al. JASN 2008

**Uremia and oxidative stress can result in neointimal hyperplasia independent of hemodynamics**

- Lee et al. NDT 2011

---

**Hemodynamic and vascular biology interactions: a challenge and an opportunity**

- Optimize Upstream Hemodynamics (Flow)

↑

Minimize Dialysis Access Dysfunction in 2010-2020

- Optimize Downstream Biology (Response to Flow)
Optimizing upstream hemodynamics and downstream biology using LOCAL therapy

**Upstream Hemodynamics**
- DEVICE 1: Optiflow
- DEVICE 2: Hybrid

**Downstream Biology**
- CELL therapy (*Vascugel*)
- DRUG therapy (*Elastase*)
- VESSEL therapy

---

Optimizing Upstream Hemodynamics: Shielding the peri-anastomotic area (Optiflow)

- Sutureless anastomotic conduit
- Reduces surgical time
- Shields the peri-anastomotic region
- Potential for changing the anastomotic angle and subsequent flow profiles

---

Excellent results as compared to historical controls

- 60 patient European study in Hungary and Greece
- Good data on an interim analysis (29 patients)

<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>14d patency</th>
<th>42d patency</th>
<th>90d patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe Study</td>
<td>100% (25/25)</td>
<td>92% (22/24)</td>
<td>83% (19/23)</td>
</tr>
<tr>
<td>Literature Control</td>
<td>n/a</td>
<td>80% (10/24)</td>
<td>68% (6/9)</td>
</tr>
</tbody>
</table>

Watch this SPACE!!!

Sutureless Anastomosis Graft

Converts an end to side anastomosis into an end to end venous anastomosis

Sutureless anastomosis graft could improve hemodynamic profile

Endothelial cell loaded gel foam wraps (*Vascugel*) for AV Fistulae (CELL THERAPY)

**Rationale**
- Endothelial cells will release beneficial mediators which will enhance dilation and reduce NH
Perivascular endothelial cell implants (Vascugel) improve patency in diabetics

Perivascular elastase administration (DRUG THERAPY)

- Recombinant elastase
- Applied to the adventitia
- Destroys the elastin in the vessel wall
- Results in a permanent increase in vessel calibre

Perivascular elastase increases AVF diameters

Tissue Engineered Grafts for AV access

Fistula First and Catheter Last!!

A Message for the Future!!

- Get away from the “one size fits all” paradigm

Individualize Vascular Access Care

- Stratify patients based on clinical and biological parameters
- Offer them the dialysis access that is best suited for them
- Individualize vascular access care through the use of novel technologies
Individualize Vascular Access Care using Novel Technologies

- 25 yr old with large veins and good endothelial function = AVF
- 50 yr old with average veins and moderate endothelial function = AVF “plus”
- 70 yr old with small veins and poor endothelial function = Graft “plus”
- 80 yr old with no veins, poor endothelial function and multiple co-morbidities = Catheter “plus”

“PLUS” = better anatomical configuration, local enhancement of vascular dilation, local anti-proliferative drug therapy, anti-infective and anti-thrombotic coatings

Not very good at stratifying patients

- Large ongoing NIH study
- Hemodialysis Fistula Maturation Consortium
- Identify clinical, biological and anatomical predictors for AVF maturation failure
- Performance of multiple endothelial function tests in over 500 patients (FMD, aortic pulse wave velocity and venous plethysmography)
- Findings from this study will allow for future stratification based on both clinical and biological inputs

Interventional Nephrology needs to Focus on Translational Research

- Unique opportunity for translational research in interventional nephrology
- Young, dynamic and growing specialty
- We have dismal survival rates!!!
- We have lots of questions and very few answers
- Our field is ideally suited for translational research with a very short bench to bedside lag time
- No one else is going to do this since no other specialty is interested in what happens when you connect an artery to a vein!!

Interventional Nephrology needs to Focus on Translational Research

- Need to embrace this opportunity
- As individuals, as a specialty (IN) and as an organization (ASDIN)
  - improve the care that we provide to our patients
  - move our specialty forward

We have the opportunity to do better – We must do better!!

Come back here Arnold; Stacey isn’t needling today!!

Dialysis Vascular Access Research Group
Multidisciplinary Collaborators

Vascular Stenosis

- Surgery (Munda and Rudich)
- Radiology (Choe)
- Pathology (Arend)
- Cardiology (Weintraub)
- Pharmacy (Desai)
- Chemistry (Meyerhoff)
- Engineering (Banerjee)

We Live in Exciting Times for Dialysis Access Stenosis!!

It was the best of times...
- Advances in molecular pathogenesis
- Advances in biomaterials and delivery technology

It was the worst of times...
- Huge clinical problem
- Growing population
- Elderly and clinically complex patients

SOLUTION

Abluminal (perivascular) drug delivery

- Endovascular device such as the "Bullfrog" micro-infusion catheter (Mercator-Med)

Tailor therapies to the biological course of vascular stenosis

Drug A initially followed by Drug B at 6 monthly intervals

Optimizing downstream biology with GENE therapy: perivascular VEGF-D (Ark)

- VEGF-D adenoviral vectors stimulate the production of NO
- Good safety data from a Phase II study
- Phase IIb trial is currently in progress

Linkages between Hemodynamics and Vascular Stenosis in the setting of dialysis access stenosis

- Seminal work by Dr Bakran’s group
- Characterised flow distribution in AV fistulae (in vitro and in vivo)

Sivanesan et al. J Biomechanics 1999
Sivanesan et al. NDT 1998
**Linkages between Hemodynamics and Vascular Stenosis in the setting of dialysis access stenosis**

- Seminal work by Dr. Bakran’s group
- Characterised flow distribution in AV fistulae (*in vitro and in vivo*)


Sivanesan et al. *J. Biomechanics* 1999

Sivanesan et al. *NDT* 1998

---

**Optimizing flow through device technology**

- Convert end to side to end to end
- Possible optimization of hemodynamics

---

**What does this really mean??**

A Mouse Is not A Man!

---

**Calculating an *in-vivo* hemodynamic shear stress profile in AVFs**

---

**AV Fistula Model (CT Angiography)**
3D Mesh Framework

AV Fistula Model: (Flow and Pressure Analysis)

Flow
Pressure

3D Wall Shear Stress Profile

Angioplasty: the Good, the Bad and the Ugly

Angioplasty
Outward remodeling due to intima-media rupture
Restenosis due to neointimal hyperplasia

Flow Patterns, shear stress rates and cellular responses

Laminar Flow and Laminar Shear Stress
Non Laminar Flow and Oscillatory Shear Stress

Happy Endothelial Cells!
Unhappy Endothelial Cells!

Shear stress induced mechanotransduction

Laminar or Oscillatory Shear

Schwartz et al. 2007
Flow patterns determine endothelial cell characteristics

Shear Stress is the most important hemodynamic factor which influences vascular remodeling

Flow patterns:
- Static
- Laminar
- Turbulent
- Polygonal
- Stellate

Davies et al. PNAS 1986

Viscous drag of blood on the cells lining the vessel wall
Directly proportional to velocity of flow and inversely proportional to the radius

STENT GRAFTS: Targeting both Hemodynamics and Vascular Biology!

- Stent scaffold enhances positive remodeling
- PTFE graft layer prevents ingrowth of myofibroblasts
- Biological systems tend to hit back
- Need long term primary patency and cumulative patency data (RENOVA)

Excellent technical results

- 10 patients
- 100% technical success
- 90% primary patency at 42d
- Phase II study ongoing in Europe

Optimizing downstream biology with CELL therapy: perivascular endothelial cell loaded gel foam wraps

- Rationale behind this approach is that the endothelial cell is not just a lining cell but also a cell that produces a slew of beneficial mediators
- Just need to deliver ECs to a site near the region of stenosis and the beneficial mediators will do the rest!

The Future is Here!
Tissue Engineered Grafts

Edelman and Nugent / J Vasc Res 2003

Haskal et al. NEJM 2010

Roy-Chaudhury et al. ASN 2009, PO-1575
**Does Gerry now want to take over Interventional Radiology as well!!**

**Venous neointimal hyperplasia is made up of myofibroblasts**

<table>
<thead>
<tr>
<th></th>
<th>SMA</th>
<th>Vim</th>
<th>Des</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMCs</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Myofib</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Fib.</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

- Migrated in from the media and perhaps the adventitia
- Response to endothelial and smooth muscle cell injury

Ray-Chaudhury et al. AJKD 2007

**Dialysis access grafts and fistulae could be the ideal clinical model for testing out novel LOCAL therapies for neointimal hyperplasia**

- Superficially located
- Away from major anatomic structures
- Easy repeated access to patients and their grafts and fistulae
- Aggressive clinical course

**VNH is characterized by significant angiogenesis**

Roy-Chaudhury et al. Kidney Int. 2001

**Perigraft macrophages play a role in VNH**

Roy-Chaudhury et al. Kidney Int. 2001

**Neointimal Hyperplasia is a Response to Vascular Injury!! (Traditional View)**

Adapted from Robbins Pathology
Whither systemic therapies: Results from the Dialysis Access Consortium

<table>
<thead>
<tr>
<th>Plavix for AVF thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 877 AVFs randomized to Plavix or placebo x 6 wks</td>
</tr>
<tr>
<td>• 6 week thrombosis rate decreased from 19% to 12%*</td>
</tr>
<tr>
<td>• No difference in suitability for dialysis (only 40%!!!)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aggrenox for PTFE graft stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 649 patients with new grafts</td>
</tr>
<tr>
<td>• Randomized to Aggrenox or placebo</td>
</tr>
<tr>
<td>• Increase in 1 year primary patency from 23% to 28%*!!</td>
</tr>
</tbody>
</table>

Dember et al., JAMA 2007
Dixon et al., NEJM 2009

*Statistically significant but clinically irrelevant!!

Houston; we have a problem!!

Post Angioplasty Primary Patency Results

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Patency Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary Angioplasty</td>
<td>90% @ 9 months</td>
</tr>
<tr>
<td>Carotid Angioplasty</td>
<td>90% @ 1 year</td>
</tr>
<tr>
<td>Iliac Angioplasty</td>
<td>70% @ 5 years</td>
</tr>
<tr>
<td>Femoral Angioplasty</td>
<td>50% @ 2 years</td>
</tr>
<tr>
<td>PTFE graft angioplasty</td>
<td>50% @ 6 months(p)</td>
</tr>
<tr>
<td></td>
<td>40% @ 3 months (t)</td>
</tr>
<tr>
<td>AVF angioplasty</td>
<td>50% @ 1 year</td>
</tr>
</tbody>
</table>

Houston; we have a problem!!

- Coronary Angioplasty 90% @ 9 months
- Carotid Angioplasty 90% @ 1 year
- Iliac Angioplasty 70% @ 5 years
- Femoral Angioplasty 50% @ 2 years
- PTFE graft angioplasty 50% @ 6 months(p)
- 40% @ 3 months (t)
- AVF angioplasty 50% @ 1 year