Vascular access in HD: strengthening the Achilles’ heel

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Vascular access in haemodialysis: strengthening the Achilles’ heel

Miguel C. Riella and Prabir Roy-Chaudhury

NATURE REVIEWS | NEPHROLOGY

Nat Rev Nephrol. 2013 Jun;9(6):348-57
Agenda

- Prevalence of types of vascular access
- Primary failure rate and pathogenesis of vascular access stenosis
- Clinical predictors of AVF maturation failure
- Pre-operative mapping
- Role of monitoring and surveillance
- Vascular access in the elderly
- Process of care
- Novel therapies
Vascular access use and outcomes

Prevalent patient cross-sections; cuffed catheters comprise 80-95% of catheter use in countries;
Figure 7: Percent of Prevalent Hemodialysis Patients with an AV Fistula in Use\textsuperscript{1}, U.S. and Networks, October 2004 and October 2010, In Comparison to FFBI Goal of 66%
Trends in vascular access type at hemodialysis initiation according to the U.S. Renal Data System

Fig. 2. Vascular access by timing of nephrology care in 2008. Data Source: USRDS Annual Data Report 2010.
Percentage of patients with central venous catheter, 2011

(6.460 / 50.128) BRAZIL

Central venous catheter 14.2%
HOSPITALIZATION IN THE ESRD POPULATION

Adjusted rates of admission for vascular access infections in the first year of hemodialysis, by month & age

Minocycline-EDTA Lock Solution Prevents Catheter-Related Bacteremia in Hemodialysis

Rodrigo Peixoto Campos,*§ Marcelo Mazza do Nascimento,† Domingos Candiota Chula,‡ and Miguel Carlos Riella*†
Figure 1. Randomization and follow-up.
Figure 2. Kaplan-Meier analysis of the probability that patients would remain free of catheter-related bacteremia (CRB) for all catheters.
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Causes of primary fistula failure

Table 2. Lesions identified

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<thead>
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<th>Type</th>
<th>Number</th>
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<tr>
<td>Accessory vein</td>
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<tr>
<td>Accessory vein + JAS</td>
<td>24</td>
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<tr>
<td>Accessory vein + proximal venous stenosis</td>
<td>6</td>
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<tr>
<td>Accessory vein + JAS + proximal venous stenosis</td>
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<tr>
<td>JAS</td>
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<tr>
<td>Proximal venous stenosis</td>
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<tr>
<td>JAS + proximal venous stenosis</td>
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<tr>
<td>Diffusely small vein</td>
<td>3</td>
</tr>
<tr>
<td>Central stenosis</td>
<td>9</td>
</tr>
<tr>
<td>Arterial anastomosis stenosis</td>
<td>38</td>
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<tr>
<td>Arterial stenosis</td>
<td>4</td>
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</table>

JAS is juxta-anastomotic venous stenosis.

Beathard et al
KI 64:1487,2003
Radiological presentation of dialysis vascular access dysfunction

- Perianastomotic stenosis
- AVF non-maturation
- Stenosis at the graft-vein anastomosis
- Graft thrombosis
Vascular access stenosis

- The major cause for AVF failure is neointimal hyperplasia

Castier Y et al KI 2006
Histological presentation of dialysis vascular access dysfunction

- Migrated in from the media and perhaps the adventitia
- Response to hemodynamic stress, surgical injury and in many cases angioplasty injury

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

Roy-Chaudhury et al. AJKD 2007
(NH2)2CO
Uremia causes endothelial dysfunction
Hemodynamic wall shear stress profile and histological stenosis
Shear Stress is the most important hemodynamic factor which influences vascular remodeling.

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

• Laminar flow with laminar shear (HIGH)
  • Endothelial quiescence
  • Minimal Oxidative Stress
  • Non-Inflammatory gene profile (Nitric oxide)

AVF/AVG
Inward remodeling
Neointimal hyperplasia

AVF/AVG
Expansive remodeling
No neointimal hyperplasia
Dialysis access stenosis is a balance between vascular remodeling and neointimal hyperplasia.

Significant Neointimal Hyperplasia + Expansive Remodeling

Original lumen size

100%

Final lumen size

200%

Mature AVF

Minimal Neointimal Hyperplasia + Negative Remodeling

Original lumen size

100%

AVF maturation failure

Final lumen size

25%

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

Expansive or outward remodeling

Successful use of AV fistula/graft

Vascular Response to Flow
Role of ESRD and CKD in the pathogenesis of vascular access stenosis
Chronic kidney disease aggravates arteriovenous fistula damage in rats

Stephan Langer¹, Maria Kokozidou¹, Christian Heiss², Jennifer Kranz¹, Tina Kessler¹, Niklas Paulus¹, Thilo Krüger³, Michael J. Jacobs¹,⁴, Christina Lente⁵ and Thomas A. Koeppel¹
CKD aggravates AVF damage

CKD aggravates AVF damage

Uremic mice have increased AV fistula stenosis

Choi et al. JASN. 2008
CKD Accelerates Development of Neointimal Hyperplasia in Arteriovenous Fistulas

Taku Kokubo,† Noriyuki Ishikawa,† Hisashi Uchida,† Sara E. Chasnoff,† Xun Xie,† Suresh Mathew,‡ Keith A. Hruska,‡ and Eric T. Choi†§
CKD Accelerates Development of Neointimal Hyperplasia in Arteriovenous Fistulas  Kokubo et al.

Severe venous neointimal hyperplasia prior to dialysis access surgery

Timmy Lee¹,²,³, Vibha Chauhan¹,³, Mahesh Krishnamoorthy⁴, Yang Wang¹,³, Lois Arend³,⁵, Meenakshi J. Mistry¹,³, Mahmoud El-Khatib¹,³, Rupak Banerjee⁴, Rino Munda³,⁶ and Prabir Roy-Chaudhury¹,²,³
Uremia and oxidative stress can result in neointimal hyperplasia independent of hemodynamics

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>% Stenosis</td>
<td>46.6 ± 9.3</td>
</tr>
<tr>
<td>I/M Area Ratio</td>
<td>0.24 ± 0.07</td>
</tr>
<tr>
<td>Average IM Thickness</td>
<td>0.34 ± 0.12</td>
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<tr>
<td>Maximal IM Thickness</td>
<td>1.16 ± 0.30</td>
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</tbody>
</table>
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-PO1696, ASN 2009
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Clinical predictors of AVF maturation failure

- small vessels (arteries <1.6 mm and veins <2–2.5 mm in diameter in particular)
- lower arm AVFs
- female gender
- obesity
- diabetes
- extensive vascular disease
- lower blood flow on the first postoperative day
- a lack of surgical experience and surgeon-specific factors
RISK OF FISTULA FAILURE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
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<tr>
<td>Age &gt;=65</td>
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<td>PVD</td>
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<td>3</td>
</tr>
<tr>
<td>CAD</td>
<td>+2.5</td>
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<tr>
<td>Caucasian</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>8</strong></td>
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</table>

Risk of Fistula Failure

Lok CE et al. JASN 17:3204,2006
Hemodynamic wall shear stress profiles influence the magnitude and pattern of stenosis in a pig AV fistula

Mahesh K. Krishnamoorthy¹, Rupak K. Banerjee¹,⁵, Yang Wang², Jianhua Zhang², Abhijit Sinha Roy², Saeb F. Khoury³, Lois J. Arend⁴, Steve Rudich² and Prabir Roy-Chaudhury²,⁵
- Higher flow rates
- Higher dilatation rates and final luminal diameters
- Neointimal hyperplasia with a minimum in tima–media thickness ratio

- Lower flow rates
- Smaller luminal diameters
- Greater differences in wall shear stress at the outer and inner vascular walls
- More eccentric neointimal hyperplasia
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Pre-operative mapping

• prior to AVF creation using cutoff values of 2 mm for the artery and 2.5 mm for the vein has therefore been strongly recommended.

• duplex ultrasound mapping: increase the use of AVFs as the access type to 63% with a primary failure rate of only 8%, (hx 14%,36%) albeit prior to the Fistula First era in the USA.
Surgical creation: when and by whom

• the single most important factor that influences AVF success or failure is likely to be the surgeon

• DOPPS data documented a lower rate of AVF maturation when AVFs were created by surgeons who had performed less than 25 AVFs during their training.
Determining AVF maturity

• AVF is assessed and examined by an experienced professional between 4 weeks and 6 weeks after its creation

• Rule of 6s: A fistula in general must be:
  • 1. a minimum of 6 mm in diameter with discernable margins when a tourniquet is in place,
  • 2. be less than 6 mm deep,
  • 3. have a blood flow greater than 600 mL/min, and
  • 4. should be evaluated for nonmaturation if, after 6 weeks from surgical creation, it does not meet these criteria.
Angioplasty: double-edged sword
By PTA, deformed circle of vessel became more real circle.
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Role of monitoring and surveillance

- **Monitoring** refers to the physical examination of a dialysis access and should be carried out in all patients (as mentioned above in the context of AVF maturation).

- **Surveillance** refers to the periodic evaluation of the vascular access using tests that may involve special instrumentation.
Role of monitoring and surveillance

- early detection of stenosis through reduced $Q_a$ and increased $VP$ should result in improved outcomes but the reality is less clear.
- randomized studies, however, did not demonstrate a beneficial effect of surveillance protocols.
Why?

1. Monitoring could be as effective as surveillance in PTFE thrombosis
3. Small changes in stenosis undetected resulting in very large decreases in access flow
• The data are somewhat clearer in the setting of AVFs

• surveillance of AVFs does in fact result in a decreased thrombosis rate.
Unadjusted thrombosis-free survival.

Flow

Control

Log Rank: p = 0.022 / Breslow: p = 0.007

Follow-up (years)

AVFs at risk:

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<tr>
<th></th>
<th>0</th>
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<td>72</td>
<td>44</td>
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<td>62</td>
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Role of monitoring and surveillance

- Surveillance in PTFE grafts: no benefit when high awareness and routine PE is done
- Beneficial when no expertise or infrastructure
Role of monitoring and surveillance

Conclusion:

• regular physical examination and clinical assessment is critical to vascular access maintenance and

• when using VP adjusted for mean arterial pressure to detect a significant stenosis, trends shown by sequential analysis should be taken into account, rather than just a single isolated measurement
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Greatest growth in incident patients older than age 65 years between red bars (1982–2000).
Figure 12: Percent of Incident Hemodialysis Patients by Age Category in Networks with Low, Moderate, and High AV Fistula Use^1
Figure 22: Percent of Incident Patients with a CVC in Use by Age Category, 2008 and 2009
Figure 22: Percent of Incident Patients with a CVC in Use by Age Category, 2008 and 2009
Individualization

• Older + minimal comorbidities + and an expectation for many years of additional survival: AVF- upper-arm AVFs may be preferable.

• Older + co-morbidities: wait until HD: PTFE graft or even a TDC
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Novel therapies

- Optiflow connector
- GORE hybrid graft
- PRT-201 Elastase
- Sirolimus COLL-R wraps
- Vascugel endothelial-cell-loaded wraps
- Paclitaxel-coated balloons
- Drug-eluting stents
- Stent grafts
- Cytografts bioengineered vessels
- Humacyte bioengineered vessels
Optimizing upstream hemodynamics and downstream biology using LOCAL therapy

Upstream Hemodynamics

• DEVICE 1: Anastomotic conduit *(Optiflow)*
• DEVICE 2: Stent Grafts

Downstream Biology

• CELL therapy *(Vascugel)*
• DRUG therapy *(Elastase)*
• DEVICE therapy *(Adventa)*
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

Manson et al. Seminars in Dialysis 2012
Gore Hybrid™ Sutureless Anastomosis Graft

Heparin bonded PTFE graft with a deployable stent graft at the venous end
Gore Hybrid™ Sutureless Anastomosis Graft

- Isolate the vein and make a nick
- Deploy stent at the venous end
- Insert the compressed stent
- Sutureless end to end venous anastomosis!
Benefits of the Gore Hybrid™ Sutureless Anastomosis Graft

- Reduces surgical injury through the creation of a sutureless venous anastomosis
- Reduces surgical time
- Shields the graft-vein intersection
- Converts an end to side anastomosis into an end to end anastomosis
Gore Hybrid™ Sutureless anastomosis graft may improve hemodynamic profile

End to side anastomosis

End to End Sutureless Anastomosis

Wall Shear Stress (dynes/cm²)

<table>
<thead>
<tr>
<th>OSI (0 – 0.5)</th>
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<tbody>
<tr>
<td>Standard End-to-Side</td>
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<td>0.25</td>
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Perivascular therapies
Endothelial cell loaded gel foam wraps (Vascugel) for AV Fistulae (CELL THERAPY)

**Rationale**

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

Primary patency

Vascugel (n=25)

Placebo (n=11)

p = 0.0054

Roy-Chaudhury et al. ASN 2009, PO-1576
Perivascular elastase administration (CHEMICAL 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

Fistula First *and* Catheter Last!!
Perivascular Sirolimus (Coll-R): (DRUG THERAPY)

Paulson et al. NDT 2012
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)

Haskal et al. NEJM 2010
Far Infra Red Therapy (Rationale)

- Increases HO-1 and reduces oxidative stress

- Decreases inflammation by reducing MCP-1

Lin et al. ATVB 2008
The MicroSyringe Infusion Catheter

- 0.014" guidewire
- balloon sheaths microneedle
- microneedle penetrates artery
- perivascular injection

Optimizing downstream biology: novel perivascular administration devices

- Endovascular device such as the “Adventa” 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

Sheathed needle

Extruded needle

Roy-Chaudhury
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
• No effective therapies

SOLUTION

Roy-Chaudhury
Thank you

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