Congenital Vascular Malformations

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Disclosure(s):

- None
• **Background & Significance:**

The often inexorable growth and expansion of congenital vascular malformations (CVMs) can result in:

• substantial morbidity

• and, in some cases, premature death of these patients
Vascular Malformations?

- Complex group of vascular lesions
- Arise by embryologic dysmorphogenesis *without* increased endothelial proliferation
Vascular Malformations?

• Lead to structural and functional anomalies of the vascular system
• Characterized by wide range of presenting symptoms and often unpredictable clinical course
Incidence: 1.2%-1.5% in general population
Etiology:
• Genetic data suggests that reduced ability to regulate the signaling processes responsible for:
  – proliferation, differentiation, maturation, adhesion and apoptosis of vascular cells

...has an important role in the pathogenesis of CVMs
Endoglin prevents vascular malformation by regulating flow-induced cell migration and specification through VEGFR2 signalling

Yi Jin¹, Lars Muhl¹, Mikhail Burmakín¹, Yixin Wang¹, Anne-Claire Duchez¹, Christer Betsholtz²,³, Helen M. Arthur⁴ and Lars Jakobsson¹,⁵

Loss-of-function (LOF) mutations in the endothelial cell (EC)-enriched gene endoglin (ENG) cause the human disease hereditary haemorrhagic telangiectasia-1, characterized by vascular malformations promoted by vascular endothelial growth factor A (VEGFA). How ENG deficiency alters EC behaviour to trigger these anomalies is not understood. Mosaic ENG deletion in the postnatal mouse rendered Eng LOF ECs insensitive to flow-mediated venous to arterial migration. Eng LOF ECs retained within arteries acquired venous characteristics and secondary ENG-independent proliferation resulting in arteriovenous malformation (AVM). Analysis following simultaneous Eng LOF and overexpression (OE) revealed that ENG OE ECs dominate tip-cell positions and home preferentially to arteries. ENG knockdown altered VEGFA-mediated VEGFR2 kinetics and promoted AKT signalling. Blockage of PI3K/AKT partly normalized flow-directed migration of ENG LOF ECs in vitro and reduced the severity of AVM in vivo. This demonstrates the requirement of ENG in flow-mediated migration and modulation of VEGFR2 signalling in vascular patterning.

Development of the blood vasculature into a hierarchical network of arteries, capillaries and veins involves tip-cell selection, migration, proliferation, mural cell recruitment, fusion of sprouts (anastomosis), lumen formation, growth and pruning. These vessel rearrangements rely on a precise coordinated behaviour of individual ECs to gain and sustain hierarchy and functionality, controlled by cell signalling and flow-mediated shear forces. The initiation and formation of new Postnatal conditional EC-specific deletion of Eng or Alk1 in the mouse leads to development of AVMs, and represents valuable models of HHT. However, while Eng LOF has a mild hyperbranching phenotype, Alk1 LOF strongly promotes tip-cell potential as well as branching. ENG and ALK1 are receptors involved in the transforming growth factor beta (TGFβ)/bone morphogenetic protein (BMP) pathway mediating downstream activation of the SMAD1/5/8
Relatively recent genetic analysis data: at least some CVMs are caused by Deregulation of VEGFA/VEGFR2/AKT signaling system controlled by cell signaling and flow-mediated shear forces.
Etiology:
• Most recent genetic data (2018):
  – PIK3CA related overgrowth syndrome (PROS)
  – Over-activation of the PI3K/AKT/mTOR or the RAS/MAPK/MEK pathway leads to:
    • Dysregulation of normal cellular functions
    • Survival advantage
    • Angiogenesis
  – is thought to be the trigger for the development and/or progression of CVMs
Pathophysiology:

- “Diffuse or localized embryologically developed errors of vascular morphogenesis leading to true structural anomalies”.
Pathophysiology:

- Extratruncular CVMs: the outcome of developmental arrest in the early stages
- Truncular CVMs: result of developmental arrest in the late stages of embryogenesis
Pathophysiology:

- Any vessel with a name = truncular
- These anomalies are treated with conventional vascular therapies and durable results
- Examples:
  - Mid-aortic syndrome
  - Persistent sciatic artery
  - ARSA/Kommerel's

Pathophysiology:

• Extratruncular malformations:
  – associated with a higher rate of recurrence and resistance to therapy
  – presumably because they possess mesenchymal characteristics of independent growth potential
Treatment Challenges:

• Nomenclature & Classification (Inconsistent terminology, archaic nomenclature)
• The paucity of established treatment guidelines
• Inadequate treatment options/strategies in the past
• Lack of understanding of CVMs lesions (from primary care physicians to subspecialists)
Nomenclature & Classification:

- Mulliken and Glowacki
- Jackson et al.
- Belov (Malan, Degni): truncal and extratruncal
- International workshop on Vascular Malformations Hamburg, Germany

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<table>
<thead>
<tr>
<th>Type</th>
<th>Forms</th>
<th>Extratruncular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predominantly arterial defects</td>
<td>Aplasia or obstructive</td>
<td>Infiltrating</td>
</tr>
<tr>
<td></td>
<td>Dilation</td>
<td>Limited</td>
</tr>
<tr>
<td>Predominantly venous defects</td>
<td>Aplasia or obstructive</td>
<td>Limited</td>
</tr>
<tr>
<td></td>
<td>Dilation</td>
<td>Infiltrating</td>
</tr>
<tr>
<td>Predominantly lymphatic defects</td>
<td>Aplasia or obstructive</td>
<td>Limited</td>
</tr>
<tr>
<td></td>
<td>Dilation</td>
<td>Infiltrating</td>
</tr>
<tr>
<td>Predominantly arteriovenous shunting defects</td>
<td>Dilation</td>
<td>Limited</td>
</tr>
<tr>
<td></td>
<td>Deep</td>
<td>Infiltrating</td>
</tr>
<tr>
<td>Combined/mixed vascular defects</td>
<td>Superficial Arterial and venous</td>
<td>Limited</td>
</tr>
<tr>
<td></td>
<td>Hemolymphatic</td>
<td>Hemolymphatic</td>
</tr>
</tbody>
</table>

Based on seventh Meeting of the International Workshop on Vascular Malformations, Hamburg, Germany, 1988.
Nomenclature & Classification:

• Historically, not primarily based on lesion physiology, leading to confusion and inconsistency about the true nature of these lesions
• Term “infantile hemangioma” has been mistakenly used to describe CVMs due to lack of understanding of these lesions
Eponymous Classification:

- Historic terms - not useful
  - hemangioma simplex
  - cavernous hemangioma
  - birthmarks (naevi)
  - port-wine stains (PWS)/”angel kiss”
  - angiomas / angiomatas
  - Klippel Trenauanay/Parkes Weber Syndrome
  - Etc.
### Congenital Vascular Malformations (CVMs)

<table>
<thead>
<tr>
<th>Type</th>
<th>Extratruncular</th>
<th>Diffuse/Infiltrating</th>
<th>Localized</th>
<th>Truncular Obstruction/Narrowing</th>
<th>Dilatation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous (VM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Arterial (AM)</td>
<td></td>
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<tr>
<td>Lymphatic</td>
<td></td>
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<tr>
<td>Arteriovenous (AVM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Capillary (CM)</td>
<td></td>
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</table>

**Significant improvement in CVM management:**

- Incorporates hemodynamic *and* anatomic characteristics
- Differentiates extratruncular vs. truncular lesions
- Clinically applicable
- Endorsed by IUP and IUA *(not ISSVA)*
Multidisciplinary Approach Rationale:

• The management of CVMs exceeds the level of expertise of any single medical specialty
• Dedicated navigator required to coordinate care
• Care requires advanced resources in many disciplines
Multidisciplinary Approach: Patient centered and lesion driven
Cynthia Shortell, M.D. – Vascular Surgery, VM Team Director
Jeffrey Marcus, M.D. – Plastic and Reconstructive, Oral and Maxillofacial Surgery
Henry Rice, M.D. – Pediatric Surgery
Charles Spritzer, M.D. – Diagnostic Radiology
Tony Smith, M.D. – Diagnostic and Interventional Radiology
Thomas Ortel, M.D. – Hematology
Eileen Raynor, M.D. – OHNS

Michael Armstrong, M.D. – Pediatric Hematology
Obinna Adibe, M.D. – Pediatric Surgery
Rose Eapen, M.D. – Otorhinolaryngology-Head and Neck Surgery
Neil Prose, M.D. – Pediatric Dermatology
Jovan Markovic, M.D. – Research Fellow
Brian Brignan, M.D. – Orthopedic Surgery
Claude Burton, M.D. – Dermatology
Jane Bellet, M.D. – Pediatric Dermatology
Deborah Semmel – Patient Coordinator
Carol Fisher – Patient and Team Coordinator
Treatment Modalities
(every patient is assigned a primary treating physician and therapeutic goals are formulated before the treatment)

r/o Vascular tumors
(Hemangiomas most common)

dceMRI
+- Arteriogram
(diagnostic and treatment planning)

CVMs

HFVMs
- Conservative
- Embolization
- Embolization + Sclerotherapy
- Resection

LFVMs
- Conservative
- Sclerotherapy
- Resection
- Multimodal

Duke Multi-D Protocol:
Treatment Modalities
(every patient is assigned a primary treating physician and therapeutic goals are formulated before the treatment)

r/o Vascular tumors
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dceMRI
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Duke Multi-D Protocol:

CVMs

HFVMs
- Conservative
- Embolization
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- Resection

LFVMs
- Conservative
- Sclerotherapy
- Resection
- Multimodal
CVMs vs. Hemangiomas:

- Initial step in the diagnostic algorithm
- Distinction between vascular neoplasms (most frequently infantile hemangiomas) and CVMs can be made based on history and clinical assessment in most cases
CVMs vs. Hemangiomas

Surgery, Injury, Hormones (Puberty, Pregnancy), No triggering factor
CVMs vs. Hemangiomas

- A rapidly involuting hemangioma
- Increased endothelial cell turnover rate (Hyperplasia)

- CVMs (do NOT regress)
- Normal endothelial cell turnover rate (Hypertrophy)
dceMRI +/− Arteriogram
(diagnostic and treatment planning)

r/o Vascular tumors
(Hemangiomas most common)

Duke Multi-D Protocol:

- Conservative
- Embolization
- Embolization + Sclerotherapy
- Resection

HFVMs

CVMs

LFVMs

- Conservative
- Sclerotherapy
- Resection
- Multimodal
HFVMs vs. LFVMs:

- Next and most critical step after tumor vs CVM distinction
- Treatment decisions and prognosis driven by this distinction
- Failure to recognize a high flow lesion or component of a lesion may be catastrophic
High Flow Vascular Malformations (HFVMs)

- “arteriovenous malformations”
- Direct connection between arterial and venous system caused by congenital malformations resulting in fistular A-V tracts
• HFVM - Physical Examination:
  • Skin discoloration
  • Elevated cutaneous temperature
  • Dilated veins
  • Thrill / bruit
HFVM - Clinical findings:
- Can be aggressive; cutaneous ischemia with ulceration, infection or hemorrhage
- Can be painful
- High output cardiac failure when extensive (rare)
US: Arterio-venous malformations demonstrate arterialized venous waveform and spectral broadening
HFVM - Diagnosis with Conventional MRI:

Arterial signal void on T2 imaging is characteristic.
HFVM - Diagnosis with Conventional MRI:

MRI: T1-weighted fat-saturated gadolinium-enhanced imaging of arterio-venous malformation reveals multiple flow voids

HFVM Diagnosis with Catheter Angiography:
Low Flow Vascular Malformation (LFVM):

- No arterial component
- Venous
- Lymphatic
- Capillary
- Combined
**LFVM Clinical Presentation:**

- Affects both superficial and deep underlying anatomic structures (skin, muscles, abdominal viscera, CNS)
- Rarely asymptomatic
- May be isolated or part of a syndrome
LFVM - Physical Examination:

- Skin discoloration
- Varicosities
- Pain
- Decreased mobility
- Swelling
- Bleeding
- Osteomuscular hypertrophy
LFVM - Primarily Venous Malformations:

- Typically bluish
- Soft and easily compressible lesions
- Usually enlarge when affected extremity is dependent or after Valsalva maneuver
Venous malformations:

- No increase in local skin temperature
- No thrill or bruit

Venous malformations demonstrate mixed (or monophasic) waveform on US
Coronal T2-weighted MRI demonstrates hyperintense signal in the venous malformation involving the anterolateral aspect of the right upper extremity.
LFVM - Diagnosis with Conventional MRI:

Axial T2-weighted MRI of the same patient

T2 coronal MRI reveals numerous varicosities and lateral draining vein in the right lower extremity of a KTS patient.
Limitations of Conventional Imaging Modalities in diagnosis of CVM:

• **Ultrasound**
  • Good for initial evaluation, bedside/clinic
  • *Imprecise* information about lesion extent and flow

• **Conventional MRI and/or CT**
  • Demonstrates the extent of larger lesions
  • Limited flow characteristics
Static MR Angiography

Useful anatomic information; NO HEMODYNAMIC DATA
Time-Resolved MRA Acquisition

- **Inflow phase**
- **Arterial phase**
- **Venous phase**

2-5 sec

Gd

2-5 min

**ROBUST HEMODYNAMIC DATA**

*and relationship to vital structures*

Courtesy of Charles Kim, MD
dceMRI: Arterial phase image demonstrates no vascular abnormality = LFVM

dceMRI: demonstrates a lesion during the arterial phase what confirms a large HFVM involving the lateral aspect of the proximal upper extremity

Evolution of dceMRI in diagnosis of CVMs

- Diagnostic modalities stratified by the frequency of use (Duke Multi-D Team) in 2011
Is dceMRI the imaging modality of choice?

- **Evaluation of dceMRI:**
  - 122 patients
  - Aged <1 to 70 years
  - 52 males (42.6%)
  - 70 females (57.4%)
  - 68 had confirmatory imaging or intervention
dceMRI was able to definitively and correctly distinguish between high flow and low flow lesion in 83% of patients

<table>
<thead>
<tr>
<th>Confirming modality</th>
<th>dceMRI determinant</th>
<th>dceMRI indeterminate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High flow</td>
<td>Low flow</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Computed tomography</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Angiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intervention/surgery</td>
<td>11</td>
<td>42</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>46</td>
</tr>
<tr>
<td>dceMRI accuracy (all lesions)</td>
<td></td>
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</tbody>
</table>

Accuracy 83.8%

underwent dceMRI. Of these, 68 had confirmatory imaging (n = 15) or intervention (n = 53). The dceMRI was able to definitively and correctly distinguish high-flow from low-flow lesions in 57 studies, for an accuracy rate of 83.8%. In the remaining 11 studies, dceMRI correctly queried flow status but not definitively, and confirmatory angiography was required.

Conclusions: Using a diagnostic tool designed to identify key clinical characteristics, we were able to successfully distinguish between high-flow and low-flow vascular malformations using dceMRI alone in 83.8% of patients, minimizing the need for unnecessary invasive catheter-based procedures. (J Vasc Surg 2012;56:757-64.)
### Table: Specificity / Sensitivity PPV / NPV

<table>
<thead>
<tr>
<th>Lesions</th>
<th>dceMRI</th>
<th></th>
<th></th>
<th>PPV</th>
<th>NPV</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>High-flow, %</td>
<td>78.6</td>
<td>85.2</td>
<td></td>
<td>57.9</td>
<td>93.9</td>
</tr>
<tr>
<td>Low-flow, %</td>
<td>85.2</td>
<td>78.6</td>
<td></td>
<td>93.9</td>
<td>57.9</td>
</tr>
</tbody>
</table>

### Statistical definitions

<table>
<thead>
<tr>
<th>dceMRI</th>
<th>+HFVM</th>
<th>No.</th>
<th>–HFVM</th>
<th>No.</th>
<th>+LFVM</th>
<th>No.</th>
<th>–LFVM</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Determinate</td>
<td>True positive</td>
<td>11</td>
<td>False positive</td>
<td>8</td>
<td>True positive</td>
<td>46</td>
<td>False positive</td>
<td>3</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>False negative</td>
<td>3</td>
<td>True negative</td>
<td>46</td>
<td>False negative</td>
<td>8</td>
<td>True negative</td>
<td>11</td>
</tr>
</tbody>
</table>

The role of dynamic contrast-enhanced magnetic resonance imaging in the diagnosis and management of patients with vascular lesions.
Is dceMRI the ideal modality?

- Differentiate between high flow and low flow lesions ✔
- Determine relationship between the VM and adjacent structures ✔
- Confer minimal risk to patient ✔
Special Diagnostic Considerations:

- Aplasia or hypoplasia of deep venous trunks
- Localized Intravascular Coagulopathy (LIC)
Special Diagnostic Considerations:

~25% Deep system abnormal

Table II. Prevalence of deep venous anomalies in congenital vascular malformations of venous predominance

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (n)</th>
<th>Phlebectasia*</th>
<th>Aplasia/hypoplasia of deep* veins</th>
<th>Aneurysm*</th>
<th>Avalvula*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belev13</td>
<td>347†</td>
<td>29/347; 8% (5%-11%)</td>
<td>71/347; 20% (16%-25%)</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Browse et al16a,16b</td>
<td>49†</td>
<td>9/49; 18% (8%-29%)</td>
<td>N/R</td>
<td>3/49; 6% (0%-12%)</td>
<td>N/R</td>
</tr>
<tr>
<td>Gloviczki et al42</td>
<td>144</td>
<td>13/144; 9% (4%-14%)</td>
<td>0/144; 0% (0%-0%)</td>
<td>N/R</td>
<td>21/234; 8% (5%-13%)</td>
</tr>
<tr>
<td>Malan11</td>
<td>234†</td>
<td>13/234; 5% (3%-11%)</td>
<td>7/144; 5% (1%-8%)</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Paes &amp; Vollmar39</td>
<td>114†</td>
<td>53/117; 46% (37%-56%)</td>
<td>2/117; 1.8% (0%-4.2%)</td>
<td>N/R</td>
<td>8/768; 1% (0%-6%)</td>
</tr>
<tr>
<td>Servedere38</td>
<td>768†</td>
<td>36/768; 4.7% (3%-9%)</td>
<td>0/768; 0% (0%-0%)</td>
<td>N/R</td>
<td>21/234; 8% (5%-13%)</td>
</tr>
<tr>
<td>Taute et al22</td>
<td>50†</td>
<td>1/50; 5% (0%-10%)</td>
<td>N/R</td>
<td>8/257; 3% (2%-6%)</td>
<td>N/R</td>
</tr>
<tr>
<td>Villavicencio et al40</td>
<td>257†</td>
<td>5/257; 2% (0%-4%)</td>
<td>N/R</td>
<td>10/257; 2% (0%-4%)</td>
<td>N/R</td>
</tr>
</tbody>
</table>

Median prevalence (%) 8/257; 2% (0%-4%)

N/R, Not reported.

*Prevalence of deep venous anomalies in patients with congenital vascular anomalies of venous predominance were estimated. The data in parenthesis represent the lower and upper limits of prevalence of the 95% confidence interval for each prevalence. The homogeneity test showed that prevalence varied significantly (P < .001).
Special Diagnostic Considerations: Aplasia or Hypoplasia of Deep System

- Evaluation of patency and anatomic variations of the ENTIRE venous system (deep and superficial)
- Assessment needs to be included in the treatment planning to avoid obliterating only vascular outflow of the extremity
• Prevalence of deep venous anomalies is even as high as 18% in patients with Klippel-Trenaunay Syndrome

Aplasia of the left iliofemoral vein segment in a KTS patient
Special Diagnostic Considerations: Coagulation Disorders in CVMs

- Coagulation disorders occur at a high frequency in patients with CVMs and are associated with potentially severe thrombo-embolic events and hemorrhagic complications.
- Localized Intravascular Coagulopathy (LIC)
  - Usually latent and asymptomatic
  - If symptomatic: associated with painful intralesional thrombotic episodes
  - Patients can become severely coagulopathic even during minor or diagnostic procedures.
Phleboliths

- Newly-formed microthrombi in LIC bind to intravascular elementary Ca\(^{++}\) deposits and form pathognomonic stone-like structures called “phleboliths”
- Phleboliths can be detected during physical examination by palpation in patients with superficial VM
- Can be detected on Xray if deep
LIC is of important clinical concern due to the potential for leading to more serious thrombo-hemorrhagic events, including:

- Deep vein thrombosis (DVT)
- Pulmonary embolism (PE) with associated pulmonary hypertension
- Disseminated intravascular coagulopathy (DIC)
Indications for treatment:

- Pain caused by LIC/Phleboliths
- Extensive Malformations
  - (surface area > 10cm²) + elevated D-dimer and/or low fibrinogen
- KTS + elevated D-dimer and/or low fibrinogen
- Marginal Vein if risk of VTE is high
- *Prophylactic prior to intervention*