Pathophysiology and Venous Ulcer Healing

Peter J. Pappas, M.D.
Clinical Professor of Surgery
Chairman, Department of Surgery
The Brooklyn Hospital
Brooklyn, N.Y.

Anatomy of Vessel Wall

Structure of Blood Vessels – 3 Layers “Tunics”

Macrovascular Disease: Varicose Veins

- Genetic
  - Primary Disease
- Acquired
  - Deep venous thromboses
  - Extrinsic Compression
- Environmental
  - Age, sex and race
  - Pregnancy and female hormones
  - Diet, bowel habits
  - Occupation
  - Height, weight and posture

Topics

- Macrovascular disease
  - Varicose Vein Formation
- Microvascular disease
  - Skin damage and venous ulcer formation
Primary and Deep Venous Thrombosis

- Primary disease has an unknown etiology
  - Responsible for 70% of all reflux cases
  - Genetics with environmental factors, such as multiple pregnancies, cause vein wall architecture changes

- DVTs cause of reflux and vein wall and valvular damage in up to 30%.
  - Thrombosis causes vein valve destruction and vein wall inflammation leading to reflux and or outflow obstruction. (i.e. post-phlebitic syndrome)

Two Hit Theory

- Valve damage leading to reflux and venous hypertension

- Vein wall damage and contractile abnormalities
Normal Venous Valve

H.F. Janssen, Ph.D. Texas Tech University Health Science Center, Lubbock, Texas. Thanks to Joe Caprini for the movie clip

Damaged Venous Valve

Thanks to Joe Caprini for the movie clip

Damaged Venous Valve

Vein Wall Damage And Contractile Dysfunction

H.F. Janssen, Ph.D. Texas Tech University Health Science Center, Lubbock, Texas. Thanks to Joe Caprini for the movie clip.
Longitudinal view of normal vein architecture

**Mechanism of clot induced vein wall injury**

 Courtesy of Tom Wakefield

Vacuolated Smooth Muscle Cells of Varicose Vein Specimen With Collagen Invasion of Media

Transverse view of Collagen Fibers In Media Of Varicose Vein
Vein wall Thickening Secondary to Clot induced Inflammation Over time

Vein wall and luminal damage

Genetic Factors

<table>
<thead>
<tr>
<th>Category</th>
<th>Males</th>
<th>Females</th>
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<tbody>
<tr>
<td>Positive-Positive</td>
<td>90%</td>
<td>90%</td>
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<tr>
<td>Positive-Negative</td>
<td>25%</td>
<td>62%</td>
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<tr>
<td>Negative-Negative</td>
<td>20%</td>
<td>20%</td>
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Microvascular Disease

Venous Hypertension: Microvascular Disease

CVI Dermal Microcirculation
Results: Immunohistochemistry Of CVI Skin For TGF-β1 and Vimentin

Results: Immunohistochemistry For TGF-β1
Leukocytes with TGF-β1 Granules

Leukocyte Diapedesis
TGF-β stimulated fibroblasts differentiate into myofibroblasts.
Injury Stimulus causes cytokine release
And RAS activation with possible
Senescence development and MMP
Synthesis

Normal wound healing process

Impaired venous ulcer healing process

Gel contraction of LC fibroblasts due to pCMV-Ras transfection

*p<0.05, **p<0.01, ***p<0.001, #: N.S. between NC & LC6
Active MMP-1,2 and TIMP-1

*MMP-1 and TIMP-1 vs MMP-2 (p≤0.01)

Compression modalities

Unna Boot

Multi layer Bandage

MMP Levels in Healthy vs Ulcer Tissue Before and After Compression Therapy

Venous Ulcer Interleukins
Venous Ulcer Interleukins

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td>TNF-alpha</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
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<tr>
<td>IFN-gamma</td>
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<td><img src="image5" alt="Graph" /></td>
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**TGF-beta**

- Elisa in 14 patients

<table>
<thead>
<tr>
<th>P values</th>
<th>Healthy vs before</th>
<th>Healthy vs after</th>
<th>Before vs after</th>
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<tbody>
<tr>
<td></td>
<td>0.05</td>
<td>0.008</td>
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**Compression and Compliance**

- Elisa in 14 patients

**Conclusions**

- Two hit theory for varicose vein formation
  - Valve damage secondary to genetic and acquired conditions.
  - Vein wall thickening and contractile abnormalities

- Microvascular Disease
  - Venous hypertension causes chronic inflammatory damage leading to venous ulceration and poor wound healing.