Evidence Summary on the Pathophysiology of Varicose Veins

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Veith Symposium 2018
New York, NY

No Disclosures

Pathophysiology of Varicose Veins

- The development of varicose veins appears to result from the complex interaction of a number of environmental, hemodynamic, and cellular processes.
- These can be roughly categorized as:
  - Hemodynamic Factors
  - Intrinsic Vein Wall Factors

Hemodynamic Factors

- Ascending Theory
  – Caudally located venous shunts overfill varicosities, causing a hydrostatic pressure column that prevents drainage of superficial veins.
- Descending Theory
  – Intra-abdominal pressure is transmitted caudally, causing dilation of superficial veins and valvular incompetence.

Hemodynamic Factors

- Valve incompetence is common.
  – >75% of patients demonstrate GSV reflux
  – >50% demonstrate segmental reflux pattern
- Known environmental risk factors suggestive of hemodynamic component in VV development:
  – Obesity
  – Multiparity
  – Occupations associated with prolonged standing
Vein Wall Factors

- Hemodynamic alterations cannot entirely explain VV pathogenesis:
  - Heritable component is clearly demonstrated
  - VV can be found caudal to competent valves.
- Weak wall hypothesis:
  - Local vein wall abnormalities precede valvular incompetence.
- Local vein wall factors likely contribute to VV:
  - Hypoxia
  - Hyperplasia and apoptotic dysregulation
  - Extracellular matrix abnormalities

Histologic Abnormalities

- Evidence of Altered Histologic Phenotype:
  - Intimal and SMC hyperplasia
  - Skip lesions
    - Areas of normal vein between ectatic areas.
    - Gross appearance either thickened and fibrotic or thinned and weak.
- Apoptosis and cellular turnover are decreased in VV segments.
  - Pro-apoptotic BAX and PARP are decreased in VV

Extracellular Matrix Abnormalities

- Studies have shown both increases and decreases in collagen and elastin
  - Likely due to skip lesions, and the difficulty in comparing across specimens.
- Disorganized ECM likely more important than total amount or ratio of Collagen:Elastin
  - Collagen fibers don’t line up straight
  - Inappropriately intercalated between SMCs
Extracellular Matrix Abnormalities

• Matrix Metalloproteinases
  – Common protease enzymes play important roles in:
    • ECM turnover
    • Tissue structural integrity
  – Clear role in the pathogenesis of Arterial Aneurysms
• Evidence is conflicting:
  – Some studies show increases in MMP-9
  – Others have shown no difference by zymography

Hyperplasia and Cellular Dysfunction

• Activation of Delta Like Ligand and Hey-2 induce SMC hyperplasia in VV1.
• Inappropriate intercalation of ECM within the SMC layer reduces contractile function.
• SMC responsiveness to vasoconstrictive stimuli is decreased2:
  • Angiotensin II responsiveness decreased
  • Phenylephrine responsiveness decreased

Local Hypoxia

• Data are conflicting regarding whether oxygen tension is in fact decreased in VV segments
• Vascular Adhesion Molecules are upregulated in hypoxia3:
  – Inflammatory cell infiltration
  – Leading to disordered ECM turnover
• Hypoxia may lead to activation of HIF-1α
  – Downstream effects on:
    • Apoptosis
    • ECM Turnover
    • Angiogenesis
  – HIF-1α is upregulated in VV vessel segments2.

Conclusions

• Complex and multifactorial
• It remains unclear whether local wall dysfunction leads to valvular incompetence or whether the reverse is true.
• Likely, VV results from imbalances in several of these factors.
Thank you