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A Treatise on Venous Diseases





Radhakrishnan N

Foreword
Valiathan MS

Contents

1. Diseases of the Venous System **1**
Classification of Venous Diseases 2
Venous Diseases of the Lower Limb 3
Anatomy 4
2. Pathophysiology of Varicose Veins of Lower Limb **13**
Biophysics 14
Cellular Changes 15
Epidemiology 16
3. Etiology of Varicose Veins **17**
Genetic Associations 18
Primary Changes in the Vein Walls and Valves 18
Normal Structure of Vein 19
Extracellular Matrix Degradation 20
Enzymatic Dysregulation 20
Activation of Endothelium 20
Smooth Muscle Cell Proliferation and Migration 21
Dysregulated SMC Apoptosis 21
4. Lymphatic System of the Lower Limb **22**
Importance of the Lymphatic System 22
Structure of Lymphatic Vessels 23
Functions of Lymphatic Vessels 23
General Principles of Tissue Fluid Formation 25
Precipitating Factors for Edema 27
5. Clinical Manifestations **30**
Clinical Complications 30
Evaluation of Patients 31
6. Staging of Chronic Venous Disease **35**
Development of Classification of CVD for Proper Evaluation 35
Revised CEAP Classification: Summary 36
Terminology and New Definitions in CVD 39
7. Management **47**
Based on Nature, Stage and Type of Problem 47
Based on Genetic and Other Factors 48

8. History of Surgical Management of Varicose Veins 51
Egypt 52
Greece 52
Rome 53
Arabia 54
Era of Barber Surgeons 55
Renaissance 56
Era of Sclerotherapy 57
Back to Invasive Procedures 60
9. Contemporary Surgical Procedures 68
Trendelenburg's Operation 68
10. Endovenous Laser Treatment 81
Evolution of EVL Technology 81
11. Radiofrequency Ablation Therapy 86
Technology of RFA 86
12. Sclerotherapy 92
Evolution of Methodology of Sclerotherapy 93
Principle of Sclerotherapy 93
Sclerosant Drugs 94
Selection of Technique 101
Complications 106
Follow-up 110
Ultrasound Guided Sclerotherapy and Endovenous Videoscopic Sclerotherapy 110
European Consensus Conference on Foam Sclerotherapy 111
13. Deep Vein Thrombosis 113
Symptoms 113
Signs 114
Wells Clinical Score for DVT 115
Complications 119
Investigations 120
Differential Diagnosis 121
Treatment 122
14. Anticoagulation in Prevention and Treatment of Venous Thromboembolism 131
Problem of VTE 131
Pathophysiology 132
Anticoagulants 137

15. Chronic Venous Ulcer **148**
Etiopathogenesis 148
Harmful Coexisting Conditions 150
Management 150
Care of the Ulcer 152
16. Morbid Varicose Vein **160**
Materials and Methods 160
Pathogenesis of Varicose Vein 163
Different Types of Varicosities 164
17. Photographic Presentation of Venous Diseases **169**

Bibliography 189
Index 213

Chapter 3

Etiology of Varicose Veins

The predisposing factors of varicose vein (VV) are usually ascribed to the following:

1. Age: As age advances, chances of development of VV increases.
2. Sex: The female hormones, estrogen and progesterone, increase the susceptibility to varicosity.
3. Pregnancy: Most commonly the manifestation of VV is seen in female during the later stages of pregnancy and is usually bilateral.
4. Profession: Nurses, traffic policemen, teachers, barmen, shopkeepers and sentry staff, who have to stand continuously for long hours, claim the development of veins due to their profession.
5. Race: In some races, there is predominance in the incidence of VV.
6. Familial: A history of many members in the same family carrying the disease.
7. Deep vein thrombosis: A block in the deep vein anywhere from leg to inferior vena cava (IVC).
8. Pelvic tumors: Large ovarian cysts, fibroid or any pelvic pathology obstructing the pelvic vein or in the inguinal region can predispose to VV.
9. Orthopedic: Prolonged immobilization in plaster cast following the fractures of lower limb, open reduction and in compound fractures.
10. Coronary artery bypass graft (CABG): When the long saphenous vein is used for the CABG, VV develop in later years.
11. Klippel-Trenaunay syndrome (KTS): Congenital aplasia of pelvic veins.

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All the factors mentioned above, in the strict sense, can be considered only as predisposing/precipitating factors in the etiogenesis of VV. Hence, there is something vital in general for the causation of this condition. A very common finding usually observed is the familial incidence of VV in close relations. A study of the genomic pattern clearly shows that more than 60% of patients give a clear association among the family members. More than 30% are unaware of the pattern of VV when they are of finer types, especially when the involvement is above knee, which usually remains symptom free. When the involvement is around the gluteal region and situated on the posterior aspect, it is very seldom noticed. Less than 10% are totally unaware or the pathology remains dormant. There is definitely a genetic factor behind the pathogenesis of VV.

GENETIC ASSOCIATIONS

Though there are various studies going on to identify the genetic association, but still it remains inconclusive. Congenital and genetic disorders are sometimes associated with varicosities. Patients with KTS present with VV, limb hypertrophy and dermal capillary hemangioma. Venous abnormalities like agenesis, atresia, valvular incompetence and venous aneurysms are seen in KTS. All these are as a result of structural abnormalities in the venous wall or in the valves. Other genetic mutation associated with VV includes *FOXC2*, which is described in patients with lymphedema-distichiasis. When these are all inconclusive, we hope for the brighter days ahead, when with exhaustive genomic studies, we will be able to identify the gene which will be a breakthrough for the elimination of this disease in the future generations.

PRIMARY CHANGES IN THE VEIN WALLS AND VALVES

While the clinical progress in the assessment and management of venous diseases remain sluggish and unremarkable, the studies in the pathological changes in the vein wall are intensive and impressive. On one side, there are intensive genetic studies and on another side, the pathologies associated with the structural, functional and biochemical changes of the venous valves and walls (Figs 3.1A to C).

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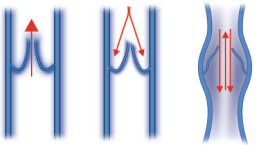
NORMAL STRUCTURE OF VEIN



Figs 3.1A to C: Normal venous valve. **A.** During dilatation of heart; **B.** During contraction of heart; **C.** Incompetent valve.

An understanding of structure of vein is important in learning the changes in the vein wall. The vein wall consists of three layers (Fig. 3.2):

1. Tunica adventitia: The strong outer covering of veins. It is composed of connective tissue, collagen and elastic fibers. These fibers allow the veins to stretch to prevent overexpansion due to the pressure that is exerted on the walls by blood flow.
2. Tunica media: The middle layer. It is composed of smooth muscle and elastic fibers. This layer is thinner in veins. The smooth muscles are arranged in a circular fashion centrally and longitudinally on either side. Smooth muscle cells (SMC) traverse through the central circular layer from the outer longitudinal layer to the inner longitudinal layer.
3. Tunica intima: The inner layer. In arteries, this layer is composed of a basement membrane and endothelium. Veins do not contain the elastic membrane lining that is found in arteries. In leg veins, the tunica intima layer gets modified to form valves to keep blood flowing in a single direction.

In smaller veins, the tunica media and tunica adventitia are very thin. In bigger veins, the tunica adventitia is very thick and the tunica media is very thin.

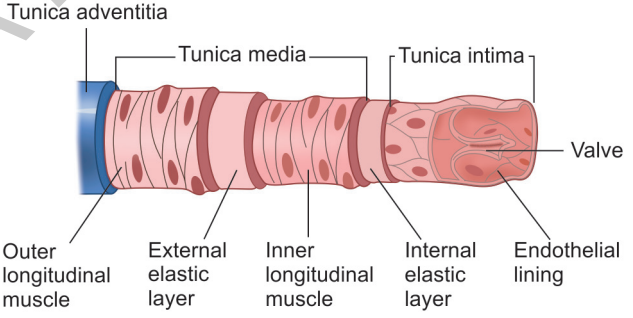


Fig. 3.2: Structure of vein

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In smallest veins, the valves are arranged very closely when compared to the larger veins. The valves fade off above the level of umbilicus.

The integrity and tone of the vessel wall depends on the cellular and extracellular matrix (ECM) components. Any degradation of these factors can lead to reduction in tensile strength of SMC of the wall and changes in the collagen content.

Numerous changes have been demonstrated in the cellular and ECM components of the vein wall in varicosity. These changes do not occur in a continuous pattern. It is usually scattered or distributed. Intimal changes include endothelial proliferation and subintimal plaque formation. The media shows SMC migration, ECM disintegration or degradation. The adventitial layer shows fibroblastic and SMC proliferation atrophied of connective tissue and loss of vasa vasorum.

EXTRACELLULAR MATRIX DEGRADATION

The ECM is the most important factor in maintaining the integrity and homeostasis of the vein through interactions with cellular components such as endothelium and SMCs, because the ECM provides a structural framework of collagen, proteoglycans, elastins, glycoproteins and fibronectins in which the cellular components are embedded. Therefore, any degradation of ECM will produce weakening and distortion of the vessel wall. Fragmentation of elastic lamina and thickening of collagen fibers are usually found in VV. The total elastin content is also seen reduced. This leads to loss of elasticity and reduction of tensile strength.

ENZYMATIC DYSREGULATION

A group of enzymes are known to regulate and maintain the homeostasis of ECM. They include matrix metalloproteinases (MMPs) and endogenous tissue inhibitor of metalloproteinases (TIMPs). MMP-TIMP imbalances have been identified in VV.

ACTIVATION OF ENDOTHELIUM

Endothelial cells have a significant role in regulating the vascular inflammation, remodeling and tone. Endothelial cells of VV are seen

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desquamated and degenerated. Such injured cells are activated and are known to release various types of inflammatory mediators and growth factors. Increased expression of inflammatory factors such as vascular cell adhesion molecule-I, intercellular adhesion molecule-I and von Willebrand factor by the endothelium of varicose compared with non-varicose vein has been recorded. There are also increased mast cells, macrophages and monocytes in VV. Activated leukocytes also release large amounts of superoxide anions and proteases that are able to degrade ECM. The release of growth factors including basic fibroblast growth factor (bFBGF) and platelet-derived growth factor (PDGF) may induce SMC proliferation.

SMOOTH MUSCLE CELL PROLIFERATION AND MIGRATION

Areas of SMC hypertrophy and proliferation occur in the tunica media of VV although areas of atrophy may also be present. Rearrangement and migration of SMCs will also be seen. SMCs in varicosities appear disorganized and dedifferentiated from contractile to synthetic and proliferative phenotype. They demonstrate vacuolization and phagocytosis. The growth factors (cell mediators) PDGF and bFBGF may also contribute to certain changes of SMCs. Estrogen and progesterone levels may also influence to some extent. The contractile strength and tone of SMCs are also impaired.

DYSREGULATED SMC APOPTOSIS

Dysregulation of SMC apoptosis also occurs. Apoptosis is a type of programmed cell death, which is characterized by zeiosis (membrane blebbing), cytoplasmic condensation, activation of endogenous endonucleases and specific proteases. It is an important physiological process in normal development, morphogenesis and tissue regulation. Apoptosis when improperly regulated leads to pathological conditions involving faulty repair of DNA mechanism and cell cycle disruption. This happens in VV.

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A Treatise on Venous Diseases

Salient Features

- Authored by a highly experienced Phlebologist
- This book is 'all about veins and venous diseases'
- New etiological and pathophysiological concepts
- Interesting history of venous surgery
- Special chapter on Sclerotherapy for varicose veins
- New outlooks and trends in the management of CVD
- Written in lucid and direct style
- Excellent clinical photographs and illustrations for better understanding
- A reference book for medical students, physicians, surgeons and all interested in vascular diseases.



Radhakrishnan N MBBS MS FAIS FIAMS graduated from Trivandrum Medical College, Thiruvananthapuram, Kerala, India, in 1969. He had his Postgraduation in General Surgery at the same college. He has put in 37 years of surgical experience. The poor results following surgical treatment of varicose veins distracted him from treating such patients. But he was destined to be a full-time Phlebologist, leaving aside all surgeries he loved most. It was incidental that he got involved slowly into this field of Phlebology in 1995 by Sclerotherapy. He crossed 17,000 procedures for varicose veins in early 2014. He could develop a Research Institute in collaboration with Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram, Kerala, India, where genomic and molecular studies of varicose veins are jointly done. The present surgical turnover is more than 3,000 annually.

It was his dream to continue his research work on venous diseases in order to prevent these diseases in the forthcoming generations, by offering research scholarships to the fellows selected by the premier institute of India, the Rajiv Gandhi Centre for Biotechnology, Thiruvananthapuram. Dr N Radhakrishnan Foundation for Research on Venous Diseases is the materialization of that dream!

He has made several national and international presentations on the topic and is appreciated for his newer outlook and approach to the disease. He has been blessed with seven national and four international awards for his commitment and dedication to his profession and community, in addition to various other awards.

He is a member of the various organizations like American Venous Forum (AVF), European Venous Forum (EVF) and also American College of Phlebology.

His surgical technique and outlook of the disease, based on microscopic venous valves (MMVs) are paradigm shifts from what was practiced for the past 55 centuries. He has several international publications (original articles) to his credit.

Shelving Recommendation
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