Venous Pathophysiology

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ABSTRACT

Chronic venous insufficiency and varicose veins are among the most prevalent medical problems in the adult population. Historically, our understanding of venous reflux disease focused upon the anatomical mechanisms of valvular incompetence. More recent investigations into the cellular and molecular aspects of venous insufficiency have shown that the disease is a complex multifactorial process reflecting both systemic abnormalities of connective tissue synthesis and cellular inflammatory reaction. New minimally invasive endovenous treatments for primary lower extremity venous insufficiency have spurred growing clinical interest in this disease. The intent of this review article is to discuss the prevalence, epidemiological risk factors, and current theories of the pathophysiology of primary venous insufficiency.

KEYWORDS: Varicose vein, venous stasis, pathophysiology

Objectives: Upon completion of this article, the reader should be able to (1) summarize the common epidemiological risk factors associated with varicose vein development, (2) understand the relationship of collagen synthesis to varicose vein formation, and (3) understand the differences of primary valvular incompetence versus primary vein wall weakness theories of varicose vein formation.
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EPIDEMIOLOGY

Prevalence

Lower extremity venous insufficiency and varicose veins are extremely common disease processes, thought to be the seventh most common indication for medical referral in the United States.[1] The exact prevalence of varicose veins remains difficult to determine because of differences in study selection criteria, disease definition, and survey methods, as illustrated by Table 1. However, based upon a meta-analysis of 21 epidemiological studies of varicose veins,[1] the overall prevalence of visible tortuous varicose veins in a Western population older than 15 years is estimated to be 10–15% for men and 20–25% for women. Table 2 summarizes the prevalence of varicose veins in various multicultural studies conducted over a 28-year period.[2]

Predisposing Factors

The development of varicose veins results from a complex interplay of multiple factors, including gender, age, heredity, parity, obesity, and lifestyle/employment.

AGE AND GENDER

Many clinical studies have shown that the prevalence of varicose veins is approximately twice as high in women as men[3–7] and increases with advancing age.[1–3,5–8] The Tampere study,[7] which examined the epidemiology of varicose veins in a large cohort of 3284 men and 3590

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Table 1 Prevalence of Varicose Veins in Males and Females from Surveys of the General Population

Year	Location	Age (y)	Method	Definition	Male (%)	Female (%)
1973	Tecumseh, USA	>10	Examination	Prominent superficial veins in the lower extremities	12.9	25.9
1981	Jerusalem, Israel	>15	Examination	Distended and tortuous subcutaneous veins, excluding very small veins (venulectasia)	10.4	29.5
1992	London, England	35–70	Questionnaire	Asked ''Have you ever had large veins or varicose veins in your legs?''	17	31
1995	Finland	>30	Questionnaire	Asked whether a physician had ever made a diagnosis of varicose veins	6.8	24.6
1999	Edinburgh, Scotland	18–64	Examination	Dilated tortuous trunks of the long and short saphenous veins and their branches of first or second order	39.7	32.2

Data modified from Fowkes et al.[2]

women, demonstrated that the prevalence of varicose veins in men and women was 18% and 42%, respectively. In this study, the overall prevalence of varicose veins at ages 40, 50, and 60 years was 22%, 35%, and 41%.

PREGNANCY

Pregnancy appears to be a major predisposing factor for the development of varicose veins and is likely a major reason why the prevalence of varicose veins is twice as high in women as in men. The development of new varicose veins occurs in up to 28% of pregnancies,[9] and the incidence rises with increasing parity. In the Tampere study, the prevalence of varicose veins in women with zero, one, two, three, and four or more pregnancies was 32%, 38%, 43%, 48%, and 59%, respectively.[7] Although the exact mechanism of pregnancy-induced venous insufficiency is not fully elucidated, it is likely that both hydrostatic and hormonal effects contribute significantly. It is theorized that the enlarged gravid uterus may obstruct the pelvic venous outflow, resulting in lower extremity venous hypertension, venous distention, and valve rupture. However, this theory is incongruous with the observations that varicose veins can appear in the first trimester, prior to significant uterine

Table 2 Prevalence of Varicose Veins by Sex in Studies from Different Countries

			Prevalence of Varicose Veins	
Year	Country	Number	Male (%)	Female (%)
1966	Bohemia	15,060	6.6	14.1
1969	Egypt	467	—	5.8
1969	England	504	—	32.1
1972	India (south)	323	25.1	—
1972	India (north)	354	6.8	—
1973	Switzerland	610	—	29.0
1975	Cook Island (Pukapukans)	377	2.1	4.0
1975	Cook Island (Rarontongans)	417	15.6	14.9
1975	New Zealand (Maori)	721	33.4	43.7
1975	New Zealand (Europeans)	356	19.6	37.8
1975	Tokelau Island	786	2.9	0.8
1975	New Guinea	1,457	5.1	0.1
1977	Tanzania	1,000	6.1	5.0
1978	Switzerland	4,529	56.0	55.0
1981	France	7,425	26.2	—
1986	Brazil	1,755	37.9	50.9
1988	Sicily	1,122	19.3	46.2
1989	Germany	2,821	14.5	29.0
1990	Japan	541	—	45.0
1991	Czechoslovakia	696	—	60.5
1994	Turkey	850	34.5	38.3

Data modified from Fowkes et al.[2]

enlargement, and that the varicose veins of pregnancy are often reversible and resolve spontaneously post partum. Ciardullo et al[10] demonstrated an association of higher serum estradiol levels with increased venous distensibility and varicose vein formation in menopausal women. Indeed, the saphenous veins contain estrogen and progesterone receptors that may enable the estradiol-rich hormonal state of pregnancy to exert a similar effect.

HEREDITY

A positive family history of varicose veins is associated with a significantly increased risk of development of varicose veins. Cornu-Thenard et al performed a case-control study of 134 subject-parent sets (67 with varicose veins, 67 controls) in which individuals and their parents were interviewed regarding history of venous disease and lifestyle and clinically examined to determine presence or absence of varicose veins. This study demonstrated that the risk of developing varicose veins was 20% with two unaffected parents,[11] 25–62% with one affected parent, and 90% with two affected parents.

BODY HABITUS

In his review of 21 epidemiological studies[1] on varicose veins, Callam concluded that obesity may be a minor positive risk factor that affects women more strongly than men. Iannuzzi et al showed that varicose veins were more prevalent in women in the upper quartile of body mass index (BMI) (> 30 kg/m^2),[12] a finding supported by the Edinburgh Vein Study, in which obesity, as defined by increased BMI, was found to be a risk factor for varicose veins in women but not in men.[13] It is postulated that subcutaneous deposition of adipose and fibrous tissue disrupts the cutaneous venous network, impairs drainage, and promotes stasis.

LIFESTYLE

Many studies support the theory that, compared with sedentary work, prolonged standing is an independent risk factor for development of venous insufficiency.[14] Three major epidemiological studies (Tampere, Edinburgh, and Framingham) independently demonstrated that varicose veins were more prevalent in individuals who stood up for the majority of the workday. In the Tampere study, the prevalence of varicose veins in standing versus sitting workers was 36% versus 27%, respectively.[7]

PATHOPHYSIOLOGY

The two most widely accepted theories of primary varicose vein pathophysiology are (1) primary valvular incompetence and (2) primary (congenital) vein wall weakness. The primary valvular incompetence theory, introduced by Sir William Harvey in 1628, postulates that varicose veins develop as the sequela of central valvular incompetence related to a paucity or atrophy of valves. This causes venous hypertension in the vein segment below, which in turn damages adjacent peripheral valves and causes propagation of varicose transformation in a central-to-peripheral direction. Although appealing in its simplicity, this theory conflicts with the facts that valves are strong structures capable of withstanding 200 mm Hg pressure without leakage or degenerative changes in leaflets[15] and that varicose veins can occur below or between competent valves.

The primary vein wall weakness theory states that varicose veins develop from a defect in vein wall integrity rather than from a problem with the valves themselves. The components of a normal vein wall include collagen matrix that provides strength, elastic fibers that provide compliance, and three smooth muscle layers (circular media surrounded by longitudinal intimal and adventitial layers) that control venous tone. Histological studies demonstrate that in comparison with normal veins, varicose veins exhibit proliferation of the collagen matrix with disruption and distortion of the muscle fiber layers.[16] In the most diseased areas, the muscle layer is completely disrupted, leaving only elastic tissue and collagen as the sole components of the vein wall. This histological alteration in turn causes loss of contractility, sagging of the muscular grid,[15] and vessel dilatation in response to venous hypertension. The characteristic serpiginous appearance of varicose veins reflects segments of dilatation interspersed between segments of normal vein.

There is increasing evidence that primary varicose veins result from an intrinsic genetic defect of collagen synthesis. In tissue culture, smooth muscle cells derived from varicose veins show increased expression and synthesis of type I collagen and decreased synthesis of type III collagen and fibronectin.[17] Skin fibroblasts cultured from subjects with varicose veins demonstrate a comparable dysregulation of collagen synthesis with excess production of type I collagen and decreased type III collagen.[18] This finding supports the theory that primary varicose veins reflect a systemic abnormality of connective tissue physiology rather than a local mechanical phenomenon at the level of the veins.

Primary vein wall weakness can lead to valvular incompetence in a process conceptualized by Edwards and Edwards in 1940.[19] In contradistinction to that of secondary varicose veins that result from post-thrombophlebitic valve leaflet damage, the mechanism of valve failure in primary varicose veins is abnormal collagen synthesis that leads to weakening and expansion of the valve annulus and in turn causes poor valve leaflet apposition and venous reflux despite relative absence of actual valve leaflet damage.[15,19] Although incompetent perforators have also been implicated as a cause of primary varicose veins, the correlation of incompetent perforators with varicose veins on pathological and

thermographic studies has been poor. Several studies demonstrate that incompetent perforator veins are larger in diameter than competent ones,[20–22] suggesting that, as with other primary varicose veins, perforator reflux develops secondarily from a primary problem with vein wall integrity. Once established, perforator reflux contributes to superficial venous hypertension, especially in the setting of concomitant deep system venous reflux.

The pathophysiology of venous stasis ulcer formation is a controversial topic that is under active investigation. It appears that the tissue damage occurs in response to a complex inflammatory reaction rather than to poor oxygen deliver to the skin as previously thought. Several possible trigger mechanisms for this inflammatory reaction have been proposed, including tissue hypoxia, humoral stimulation, and, most recently, a shift in fluid shear forces at the endothelial level related to venous hypertension. Once initiated, the inflammatory process results in up-regulation of endothelial attachment proteins; sequestration of activated leukocytes in the capillaries and postcapillary venules; migration of mast cells, monocytes, and lymphocytes into the connective tissues; and increased oxygen free radical production and humoral activation that result in parenchymal cell death.[23,24]

EFFECT UPON QUALITY OF LIFE

The impact of venous insufficiency upon quality of life (QOL) was investigated by the Venous Insufficiency Epidemiological and Economical Study (VEINES), an international survey. In VEINES, 65.2% of subjects with varicose veins had additional venous disease processes (edema, skin changes, ulceration), and both physical and mental QOL scores decreased as the severity of concomitant venous disease increased. In the most severe cases—those in which venous ulceration was present—the QOL rating was worse than with chronic lung disease, back pain, or arthritis.[25,26]

SUMMARY

Venous insufficiency is a very common problem, present in 20% of the adult population, and likely to increase in prevalence as medical advances extend human longevity. Contrary to the historical opinion that varicose veins are the sequelae of simple mechanical valve failure, there is growing evidence that the pathophysiology of primary venous insufficiency is a complex process, reflecting an interplay between systemic dysregulation of connective tissue synthesis, mechanical forces of venous hypertension, and cellular inflammatory reaction. Superimposed upon these biological processes is a highly varied combination of physiological and socioeconomic issues including gender, age, employment, and body habitus. Continued research into the physiological, mechanical, and microcellular aspects of venous insufficiency is critical to limiting its impact as a cause of major morbidity, quality of life impairment, and potential health care expenditure.

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