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Pathogenesis of Varicose Veins

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Background: *varicose veins are present in up to 40% of the population. They may be associated with considerable morbidity. Around 70% of patients with chronic venous insufficiency have evidence of superficial venous incompetence on duplex imaging.*
Methods: *in this publication we review the evidence available regarding the pathogenesis of varicose veins.*
Results: *a number of theories have been suggested. The present data suggests that abnormalities in the venous endothelium and smooth muscle cells result in vein wall dilatation with secondary valvular incompetence. However, there is also evidence to support acquired venous valve failure. Congenital venous valve abnormalities have not been well studied.*
Conclusion: *further work is required on this relatively neglected topic. The use of improved imaging such as high-resolution ultrasound is likely to significantly improve our understanding of venous valve function and pathology.*

Key Words: Varicose veins; Pathogenesis.

Introduction

Varicose veins (tortuous, twisted, or lengthened veins) are present in 10–40% of 30–70 year old people.[1,2] The majority of patients associate their varicose veins with a number of symptoms, including cosmetic embarrassment, leg aching, puritus and skin rashes, although the exact relationship between such complaints and objective varicosity is far from clear.[1,2] A proportion of patients will go on to develop serious complications of their varicose veins, including superficial or deep thrombosis, skin thickening and staining (lipodermatosclerosis), haemorrhage from a superficial varicosity or ulceration.[3] The exact incidence of these complications in patients with varicose veins is not known for a number of reasons. Firstly, the great majority of the population with this condition do not present for medical treatment. Secondly, longitudinal studies of patients with uncomplicated varicose veins are rare and would need to be large and over a period of 20 years or more to provide this information.

Lower limb ulceration is responsible for considerable morbidity and health cost.[4] Around 70% of lower limb ulcers are due to venous disease.[5] The aetiology of skin damage in venous disease is incompletely understood, however, venous hypertension consequent on venous valve incompetence is believed to be of paramount importance.[6] Therefore, at present the management of varicose veins principally rests on the identification and treatment of valvular incompetence. Duplex ultrasound studies demonstrate that 30% of patients with venous ulcers have superficial venous incompetence only, while a further 40% have superficial reflux in combination with deep vein valvular incompetence.[7] Despite large numbers of ultrasound studies on patients with venous insufficiency relatively little work has been concentrated on the pathogenesis of the venous disease.

Methods

Data from papers dealing with varicose vein pathogenesis were sought by searches performed on PUBMED and MEDLINE. In addition hand searching based on references from identified publications was carried out. Due to the diverse nature of techniques that may be used to provide evidence for varicose veins pathogenesis wide search criteria were employed. Keywords used were varicose veins, pathogenesis, pathology, endothelium, smooth muscle, duplex, and epidemiology. Numerous publications dealing with duplex imaging were identified but only selected for further assessment if they provided evidence to support or refute one of the theories

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of varicose veins pathogenesis. Relatively few papers dealing with the vascular biology of venous disease were identified and these were all included for detailed assessment.

Epidemiology

For a detailed discussion of the epidemiology of varicose veins readers are referred to an excellent review.[2] The suggested risk factors for varicose veins include female gender, age, pregnancy, family history, race, occupation, obesity and diet.[8–11] Firm conclusions regarding the importance of these factors in the aetiology of varicose veins is hampered by the variable methods which have been used to define varicose veins, sample the population and record risk factors.[2] Critical analysis of the data available on epidemiology suggests that older age, multiple pregnancies and Caucasian race are the most well supported risk factors for varicose veins.[2] Most studies have suggested varicose veins are more common in women, with a female to male ratio of between 1.5:1 and 3:1.[2] However, a recent study by Evans and colleagues reported equal incidence of varicose veins in men and women.[8] There is little evidence to support other factors such as family history and occupation.[2] The recent Edinburgh vein study investigated 1566 men and women and found a weak association between standing, straining at stool, and height with superficial venous reflux.[12] The importance of these factors in the development of varicose veins is difficult to clearly define as studies have given conflicting findings. The authors of the Edinburgh vein study concluded that there were no strong and consistent life style risk factors for venous reflux.[12]

Lessons from duplex studies: What is the relationship between deep and superficial reflux and what is the role of thrombosis in superficial reflux?

Classically varicose veins arising as a result of an identified cause such as previous DVT are referred to as secondary. However, in the majority of cases there is no identifiable cause for the development of the varicose veins, which are therefore referred to as primary. It is normal for blood to flow down the superficial or deep veins for up to a second under conditions that stimulate valve closure, such as standing.[13] The cut off point at which incompetence is defined is rather arbitrary. However, studies in normal people suggest that 95% of "physiological" reflux has stopped by 0.5 s when valvular integrity is determined by distal compression in the standing position.[13] Hence this period of reflux is used by many sonographers to define venous incompetence. Using these criteria Labropoulos and colleagues demonstrated venous incompetence in 11 of 80 normal limbs, in patients aged 15–35 years. In people with prominent but not varicosed veins the incidence was as high as 77%.[13] The site of reflux was distributed throughout the leg, but the principal location was the great saphenous vein. Studies from patients with superficial reflux without a history or evidence of DVT demonstrate associated deep venous reflux in around 20% of patients.[14] In some cases this reflux appears to be limited to the region of the superficial and deep connection, and resolves following correction of the superficial reflux.[14,15]

Following DVT the incidence of superficial as well as deep reflux appears to be increased according to the study of Meissner and colleagues.[16] They carried out repeat duplex imaging on 69 limbs in which a DVT had occurred. Thrombus was demonstrated in the great saphenous vein (GSV) initially in 21%. At 8 years the incidence of GSV reflux was 29% in limbs that had developed a DVT, compared to 15% in the contralateral limb.[16] The reflux incidence was much higher in limbs in which the initial thrombosis had involved the GSV (77%). The importance of thrombus as a prelude to valvular incompetence is supported by studies following the outcome of DVT[17–23] (Table 1). These studies demonstrate early recanalisation of thrombosed vein segments, however, valvular incompetence often develops at the site of thrombus formation. Reflux that develops at other sites in these patients is likely multi-factorial, resulting from proximal occlusion leading to venous dilatation, secondary thrombosis at other sites and other primary factors (see below). There is increasing evidence that subclinical deep vein thrombosis occurs. For example in a recent randomised controlled trial of healthy travellers over 50 years of age, asymptomatic calf vein thrombosis was detected in 10% of people not wearing support stockings.[24] It is likely that if these patients had not been part of a duplex study this problem would have gone undetected. Thus it is possible that sub-clinical thrombosis involving the deep or superficial veins may have a role in the aetiology of primary varicose veins.

Theories of primary varicose veins aetiology

Congenital or acquired valvular dysfunction

Estienne and Canano discovered the venous valves in the 1530s.[25] Initially it was suggested that valvular

Table 1. Selected studies of DVT by duplex imaging.

Author	Limbs	Follow-up (months)	Recanalisation (Partial or complete)	Reflux at site of thrombosis	Reflux at other sites	Predictors of CVI*	Incidence of CVI* (grade 4–6)
17	70	24	99%	NA	NA	Proximal thrombus, greater thrombus and maintained outflow obstruction	30%
18	63	12	87%	NA	NA	NA	NA
19	158	12	77%	NA	NA	NA	NA
20	73	55	95%	NA	NA	Severity of reflux	21%
21	58 (calf)	36	88%	9%	30%	NA	NA
22	72	120	99%	46% (proximally)	25% (proximally)	NA	NA
23	27	34	96%	54/120 (45%)	3/40 (8%)	NA	NA

NA = not available.
* CVI = Chronic venous insufficiency, grade 4–6 by the CEAP classification.

failure at the sapheno-femoral junction was the primary event with secondary failure of more distal valves as a result of the increased pressure placed on these sites.[26] However, the finding of isolated valvular incompetence at distal sites or tributaries disproved this idea.[14] For example Labropoulos and associates studied the site of superficial valvular incompetence in 139 limbs with primary reflux.[14] In 24% reflux was detected in the main trunk of the great saphenous or a tributary without junctional incompetence. This does not, however, rule out a primary valvular problem that develops at a variety of sites. There have been remarkably few pathological studies of valves in venous disease. Ono and colleagues studied great saphenous vein removed from patients with duplex demonstrated valvular incompetence.[27] They found clear valve leaflet shortening in three of seven specimens examined. In addition, they demonstrated monocyte/macrophage infiltration at valve sinuses. These findings were absent in the four specimens of macroscopically normal vein removed from patients undergoing coronary bypass. Such leukocyte infiltration could be an important factor in the generation of valve damage and development of incompetence by the induction of fibrosis. However, it is possible that the inflammatory focus is a secondary phenomenon, especially as it does not appear that patients with previous thrombophlebitis were excluded. Sub-clinical thrombosis is another possible mechanism by which valvular incompetence might develop. Interestingly a recent association has been demonstrated between polymorphism in the gene for the anticoagulant protein thrombomodulin and varicose veins.[28] A more recent pathological study of 65 proximal great saphenous valves excised at varicose vein surgery demonstrated widening of the valve annulus associated with medial hypoplasia in the majority of cases.[29] Whether these changes result from a primary valve problem or primary medial problem is unknown. Improved imaging is likely to be required to resolve this issue. A study by Yamaki and colleagues correlated the findings on pre-operative duplex imaging with those demonstrated intra-operatively by angioscopy.[30] By endoluminal imaging they defined three groups of valve cusp abnormalities in 75% of patients and absent sapheno-femoral valves in 25%. While duplex could be used to detect these abnormalities with high sensitivity, the specificity in defining the type of cusp problem was low.[30]

Primary venous dilatation leading to secondary valvular incompetence

Structural weakness of the vein wall. This theory has recently received most support. A primary weakness in the wall of the vein could result in dilatation of the vein with resultant separation of valve cusps and eventual reflux. Most authors have suggested that this weakness would be a result of structural problems in the wall of the vein.[31–35] A number of abnormalities in the structural proteins of the vein have been demonstrated. These include abnormal collagen and elastin content, intimal hyperplasia and changes in matrix controlling enzymes, although the changes demonstrated have varied from one study to another.[31–35] Andreotti and colleagues demonstrated a reduction in both collagen and elastin content in varicose compared to macroscopically normal veins.[31] They also found alterations in the collagen content of skin taken from patients with varicose veins and suggested a systemic collagen disorder in varicose veins.[32] In contrast, most investigators have found an increase in the collagen content of segments of varicose compared to normal veins.[33,34] For example, Gandhi *et al.* demonstrated an increase in the collagen content, decrease in the elastin concentration, without change in the activity of proteolytic enzymes in the wall of varicose veins.[33] Sansilvestri-Morel *et al.* found an imbalance in the sub-types of collagen synthesised by smooth muscle cells derived from varicose veins.[34] Collagen type I was increased

while type III was decreased. Badier-Commander and colleagues recently investigated the concentration of enzymes regulating the extracellular matrix in specimens from patients with varicose veins.[35] They discovered a relatively high concentration of the tissue inhibitor of metalloproteinase, TIMP-1, and a relatively low concentration of the proteolytic enzyme, metalloproteinase 2.[35] This balance of matrix controlling enzymes would favour the accumulation of matrix within the wall of varicose veins. Interestingly, inflammation is normally associated with a proteolytic enzyme environment.[36] Thus to date the matrix changes demonstrated in the wall of varicose veins have not been consistent in different studies. This may relate to the fact that many of the pathological findings are the result rather than the cause of the development of varicose veins.

Impaired venous tone. Another possibility is that the dilatation results from inability of the vein to contract adequately as a result of smooth muscle cell or endothelial dysfunction. In support of this theory a number of abnormalities in the contraction and relaxation of varicose vein have been demonstrated compared to normal vein.[37–41] Duplex studies suggest reduction in vein wall elasticity in patients with varicose veins.[37] Brunner *et al*. assessed the contraction of grossly varicosed vein in comparison to vein mildly varicosed and competent vein from the same patient.[38] They discovered that phenylephrine induced contraction was absent in the overtly varicosed segments. However, of note the incompetent but macroscopically normal vein contracted normally, suggesting that a primary contractile abnormality, in response to phenylepherine at least, was not an early event in the aetiology of valvular incompetence. Mildly varicosed segments had normal endothelial-dependent relaxation but reduced endothelial-independent relaxation to nitroprusside suggesting a global dysfunction of the smooth muscle in varicose veins. In support of this, in a culture model of varicose veins smooth muscle cells appear to be heparin resistant compared to cells from normal vein.[39] Other investigators have demonstrated reduction of endothelin B receptors in varicose veins.[40] Other functional abnormalities have also been detected and include reduction in nitric oxide and vascular endothelial growth factor release under conditions of venous hypertension.[41] Changes of venous tone have been documented in pregnancy.[42–44] Studies using duplex imaging report an increase in diameter of the main superficial veins from the first to the third trimester.[42,43] These diameter changes are associated with a greater number of patients having valvular incompetence.[42,43] The changes return to baseline after pregnancy but suggest a definite hormonal effect on venous tone. Interestingly both oestrogen and progesterone receptors have been demonstrated in saphenous vein.[44,45]

Endothelial activation. Michaels *et al*. suggested that in venous insufficiency stasis results in endothelial hypoxia with secondary activation.[46] Certainly there is some evidence of endothelial activation in patients' with venous disease. For example increased expression of the endothelial adhesion molecules ICAM-1 has been demonstrated in varicose veins.[47] A study by Biagi and colleagues suggested that varicose vein produced less prostacyclin but more thromboxane A2 and prostagladin E2.[48] These changes would favour platelet activation and thrombosis. However, Nemcova *et al*. were unable to confirm these findings in a more recent study.[49] In a detailed study by Badier-Commander and associates the concentration of fibroblast growth factor and transforming growth factor beta were found to be increased in atrophic varicose veins segments.[50] These changes may contribute to the smooth muscle cell hypertrophy that occurs in some varicose segments.

There is evidence for interaction between leukocytes, platelets and the endothelium in thrombus formation[51] thus it is possible that alterations in the endothelial phenotype have an important influence in thrombosis and varicose vein formation. For example serum levels of the adhesion molecule VCAM-1 are elevated in patients with recent DVT.[52] Interestingly experimental venous hypertension is associated with a rise in the serum concentration of the soluble adhesion molecules E-selectin, ICAM-1 and VCAM-1.[53] This change is more marked in patients with chronic venous insufficiency. The endothelium is also fundamental in control of vasomotor tone, for example by the production of nitric oxide, endothelial derived hyperpolarising factor and endothelin. Changes in endothelial derived vasoactive compounds may also be an influential factor in the development of varicose veins (see above).

Increased arterial inflow associated with multiple arteriovenous communications

Arteriovenous communications in patients with varicose veins have been reported in angiographic studies and microsurgical dissections.[54,55] Further support for the presence of arteriovenous shunt in varicose veins comes from studies reporting increased oxygen partial pressures in the saphenous vein of varicosed compared to normal veins.[56,57] The inability to demonstrate such fistulae during sapheno-femoral ligation to treat varicose veins has led to little promotion of

this theory and limited investigation has been carried out to prove or refute the mechanism.

In conclusion the pathogenesis of venous disease has been relatively under investigated. Epidemiological studies have failed to show strong associations between environmental factors and varicose veins, however, increased age, Caucasian race and multiple pregnancies do appear to increase the risk of varicosity. Pathological studies demonstrate abnormalities within the venous wall in endothelial cells, smooth muscle cells and extracellular matrix as important mechanisms in the development of venous incompetence. It is also likely that direct valvular pathology occurs possibly in association with inflammation and sub-clinical thrombosis. An improved understanding of venous valvular function and pathology awaits increased application of modern imaging, such as high-resolution ultrasound.

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