Journal of
Vascular Surgery
Venous and Lymphatic Disorders™

REVIEW ARTICLES

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A different way to look at varicose veins

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Objective: **The development of varicose veins is commonly attributed to vessel wall degeneration. The idea that varicose veins occur because of pathological processes, however, is challenged by certain observations. For example, their high prevalence (50% or greater) in many populations makes it statistically "normal" to have varicose veins; their well-established genetic predisposition raises the possibility that this high prevalence reflects a survival benefit. One way to explain this apparent contradiction is to theorize that varicose veins are produced by the same mechanism(s) that lead to the growth and remodeling of other types of blood vessels. If so, being "good" at forming varicose veins may also predispose to being "good" at forming various types of collateral blood vessels when necessary.**

Methods: **A selected literature review was conducted. Works chosen for review included those suggesting that: the process of varicose vein formation may share the same basic mechanisms as the formation of collateral veins, arteries, and lymphatic vessels; and clinical outcomes may be different between subjects with and without varicose veins.**

Results: **Evidence suggests that subjects who are "good" at forming varicose veins may also be "good" at forming various types of collateral vessels, and they may have better overall survival (with less cardiovascular morbidity) than those without varicose veins.**

Conclusions: **Varicose veins may be "the price we pay" for an enhanced ability to form collateral vessels when necessary. (J Vasc Surg: Venous and Lym Dis 2014;2:207-11.)**

Varicose veins are common. Although the general public typically thinks of them as the large, bulging blue snakes slithering up Grandma's legs (or worse, their own legs), vein experts usually favor a broader definition; for example, the Vascular Disease Foundation defines varicose veins as "enlarged (dilated), elongated, and twisted veins, usually found in the thighs and legs, ranging in size from small spider veins to very large bulging rope-like veins."[1] According to the Edinburgh Vein Study, approximately one-third of subjects between 18 and 64 years of age have large "trunk varicosities," and more than 80% have smaller reticular or intradermal varices[2]; based on these definitions and demographic data, one can argue that varicose veins are (at least statistically) "normal" and that it is technically "abnormal" to lack them. The sheer magnitude of varicose veins in the modern world poses a pathophysiological dilemma and raises certain theoretical questions. For example, if more than half the population has varicose veins, is it accurate to characterize them as "abnormal" — or even, as some assert, a "disease?"[3] Why do so many people have these "abnormal" veins? If varicose veins are abnormal, are they necessarily "bad?" Is it possible that varicose veins are more benign than generally assumed — or perhaps paradoxically beneficial in some circumstances?

We can address these questions by examining aspects of the literature that pertain to the formation of primary varicose veins, secondary (collateral) varicose veins, collateral arteries, and lymphatic vessels. By reinterpreting currently available data, it is possible to challenge the notion of varicose veins as a "disease" and offer the alternative hypothesis that varicose veins may develop as logical (if undesirable) "side effects" of various genetic traits that normally promote general vascular growth and/or remodeling. Although "varicose veins" are undesirable, the genetic traits that promote their formation could be beneficial in situations where it is desirable to grow new blood vessels or remodel existing ones.

WHAT CAUSES VARICOSE VEINS?

Most authorities attribute varicose vein formation to some combination of three factors: venous hypertension, genetic factors, and acquired factors.

Venous hypertension. Humans are bipeds. We walk upright. This form of locomotion is unique in the animal kingdom. One consequence is that the (upright) venous pressure in our legs and pelvis is relatively high. According to most theories of varicose vein formation, this high pressure contributes over time to venous valve failure and/or

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Author conflict of interest: none.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the Journal policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

2213-333X/$36.00

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http://dx.doi.org/10.1016/j.jvsv.2013.08.006

the chronic dilatation and enlargement of veins; it helps to explains why we tend to develop varicose veins in our legs or pelvis and not, for example, in our arms.

The contribution of venous hypertension to the formation of varicose veins may not be solely a matter of excessive orthostatic pressure; indeed, venous hypertension poses a classic "chicken or the egg" dilemma with regard to varicose vein formation. Various venous pumping mechanisms (eg, the calf muscle pump) normally act to empty the veins and decrease venous pressure during ambulation. If, on the one hand, these pumps fail for any reason (acquired venous obstruction, valvular damage from phlebitis, neuromuscular dysfunction, etc), ambulatory venous pressure will be higher than normal, and varicose veins may form as a result — in this scenario, varicose vein formation occurs secondary to pump failure. Alternatively, varicose vein formation may be the primary inciting event (ie, some unspecified process causes veins to dilate and/or valves to become incompetent; the subsequent reflux leads to a vicious cycle of pump failure, further impairment of venous emptying, and additional development of varicose veins).

Genetic factors. The idea that varicose veins develop on a genetic basis is well-accepted.[4] For certain pathological entities like the Klippel-Trenaunay-Weber syndrome, the genetic basis for vascular anomalies (including varicose-type veins) is dramatic and indisputable. The link between genes and vascular anomalies for other conditions may be more subtle, and in many cases, the relationship can seem tenuous and inconsistent; for example, why does someone with a genetic anomaly (for example, Klippel-Trenaunay-Weber syndrome) typically develop vascular manifestations only at certain sites — perhaps a single limb or organ — when the predisposing genetic defect presumably affects DNA everywhere? Although most varicose veins are not associated with identifiable genetic syndromes, even the most unobservant practitioner recognizes that a familial predisposition to form varicose veins exists. Specific genes and/or genetic products associated with varicose veins have been identified[5] and include, but are not limited to, vascular endothelial growth factor, matrix metalloproteases (MMPs) and their inhibitors, FOXC2 genes, NOTCH3 genes, thrombomodulin promotor genes, transforming growth factors (TGFs), and many others.[6-10] The precise pathophysiological role of these and other factors affecting collagen (both the amount and subtypes produced), elastin, and other basic elements of the vein wall are currently areas of active venous research.

Acquired factors. Varicose vein formation may be induced or aggravated by trauma, inflammation, or other influences that are not genetic in origin. For example, venous thrombosis (with acute inflammation and subsequent chronic recanalization) is widely recognized as a triggering event for varicose vein formation. Nonthrombotic causes of inflammation such as the "rolling leukocyte" model of mural inflammation have also been proposed as potential pathogenic mechanisms.[11]

Some factors are neither purely genetic nor purely acquired, including those that induce or promote vascular proliferation (ie, angiogenesis or vasculogenesis). These include factors such as estrogen; it is well established that varicose veins develop and grow under the influence of estrogens.[12] This observation may help to explain why pregnant and perimenopausal women, those with liver disease (who lack the ability to metabolize estrogen efficiently), and many others with abnormal estrogen metabolism are prone to the formation of varicosities. Other factors, many of which are unknown or unstudied at present, likewise promote venous proliferation (eg, poorly characterized factors promote the formation of generalized telangiectasis in patients with certain cancers such as lymphoma[13]).

The relationship between genetic or acquired factors and venous neogenesis, proliferation, or remodeling can be even more complex in certain congenital syndromes with vascular features. For example, conditions associated with the RASA 1 mutation (eg, Parks-Weber syndrome) typically have localized areas of vascular/venous proliferation and remodeling contiguous with (or downstream from) fast-flow arteriovenous malformations (AVMs). The mechanisms producing the observed changes in venous structure are uncertain. Perhaps RASA 1 mutation exerts a direct effect on nearby veins — an effect that causes them to enlarge, remodel, and/or proliferate through the same mechanism(s) that promote the formation and growth of AVMs? Or is the influence of the RASA 1 mutation limited solely to the formation and growth of AVMs? If so, the development of venous changes may be nothing more than the subsequent response of nearby veins to high flow and volume overload. Or do these (and possibly other?) mechanisms contribute to venous remodeling and growth in a multifactorial fashion?

Other congenital conditions, including many that are not associated with RASA 1 mutations, are also associated with high- or low-flow regional areas of varicose-like venous changes; examples include Paget-Schroetter syndrome, Hereditary Benign Telangiectasia, Sturge-Weber syndrome, Klippel-Trenaunay syndrome, and others. An analysis of all the known (and theoretical) ways in which the genetic abnormalities associated with these and other conditions might potentially influence venous structure and function is beyond the scope of this work, but it is clear that the relevant relationships remain complex and incompletely understood.

The factors that cause varicose veins are "bad." Conventional wisdom maintains that the factors causing varicose veins — venous hypertension along with acquired or genetic factors, — are intrinsically "bad." For example, venous hypertension (which patients typically attribute to things like "I was forced to stand so much at my job…") and superficial phlebitis (acquired as the result of trauma, prolonged immobility, or hypercoagulability) are (1) commonly thought to contribute to varicose vein formation and (2) obviously bad. Conventional wisdom also suggests that varicosities occur in some individuals — but not in others — because some people are cursed with bad genetics that cause varicose veins, while others are not.

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