

Primary varices pathogenesis. The appealing unitary model

F. Calotă¹, I. Vasile¹, S. Mogoantă¹, C. Meșină¹, M. Pașalega¹, L. Rusu³, E. Moraru¹, M.C. Stoicea², C. Mirea¹, D. Camen⁴

¹The IInd General Surgery Clinic, Emergency County Hospital of Craiova

²Hystopathology Laboratory - Emergency County Hospital of Craiova

³Sports and Kinetotherapy Faculty, University of Craiova

⁴“Dr. Camen” Clinic

Rezumat

Patogenia varicelor primitive. Tentația modelului unitar

Patogenia varicelor primare numite și varice gravitaționale sau hidrostatice este încă neelucidată în ceea ce privește evenimentul declanșator sau progresia bolii. În timp au fost emise mai multe ipoteze care să explice fenomenele mai sus menționate. Evoluția tehnologică actuală a permis progrese evidente în descifrarea mecanismelor venoase, clarificând fiziopatologia venoasă prin evidențierea hemodinamicii venoase, a modificărilor parieto-valvulare și a progresiei lor în dinamică. Importanța stabilirii unui model patogenetic unitar, complet derivă din posibilitatea stabilirii unei terapii corecte, rapide, adresată mecanismului patogenetic al bolii (corectarea “porții de pierdere presională”), corelată cu stadiul evolutiv (gradul de reflux) și tipul de varice primare (gravitaționale, non-gravitaționale, varice “suspendate”). Inițial, studiul nostru a demarat ca o evaluare critică a modelului patogenetic clasic. Ulterior, bazându-ne pe o bogată experiență acumulată, am formulat un nou model patogenetic evolutiv, unitar și complet în varicele primare, susținut prin dovezi solide și verificat prin rezultate terapeutice.

Cuvinte cheie: varice gravitaționale, non-gravitaționale, varice “suspendate”

Abstract

Primary varices pathogenesis is still unclear about the trigger event and the disease progression. Throughout time, a lot of hypotheses were created, each with a certain degree of veracity, to explain the aforementioned dilemmas. Present day investigation technologies allowed the undeniable progress in deciphering venous mechanics and biochemistry. Objectifying venous hemodynamic and valvular-parietal changes, their dynamic progression as well, lead to important clarifications in primary varicose disease physiopathogenesis. The importance of establishing a complete, unitary pathogenic model implies the practical possibility of immediately applying the right therapy addressing the pathogenic mechanism of this disease (i.e. correcting the “pressure escape” gateway) correlated with the progression stage (reflux degree) and the type of primary varices (gravitational, non-gravitational, or “suspended” varices). Initially, our study produces a critical evaluation of the classic pathogenic hypotheses and, later on, based on our long time experience in this field, it presents a complete and unitary, evolutive and pathogenic model in primary varices. The proposed model details a pathogenesis and a progression far more nuanced in primary varices, based on solid evidence, having obvious therapeutic implications and predictable results.

Key words: gravitational varices, non-gravitational varices, “suspended” varices

Corresponding author: Prof. dr. Calota Firmilian
Emergency County Hospital of Craiova,
no. 1, Tăbaci Street, 6th floor,
The IInd General Surgery Clinic
E-mail: ssmogo@yahoo.com

Primary varices, also called gravitational or hydrostatic varices, are irregular dilatations of the superficial veins, with sinuous courses caused by the complete destruction of parietal and valvular structures under disturbed hemodynamics. Varices

indicate a failure to adapt to the gravitational force, in orthostatism, of certain venous segments in the lower limbs with constitutional or acquired phlebopathies. Following a prolonged physiopathological process, difficult to monitor, still incompletely understood, primary varices, as clinical expression and evolutive stage in the chronic venous disease, do not have a unitary pattern of debut and progression.

A critical evaluation of classic pathogenic hypotheses

Classic pathogenic hypotheses explain primary varicose disease and its major clinical expression (i.e. varices) as a consequence of structural modifications that, secondarily, cause important hemodynamic disturbances. These disturbances, in turn, aggravate the structure and functions of the venous system in the lower limbs, thus closing a vicious circle.

The following pathogenic structural hypotheses, trying to explain the mechanism behind primary varices, are best known:

- hypotheses incriminating the venous wall (parietal defect → secondary hypotonia → valvular insufficiency → reflux);
- hypotheses incriminating the valvular system (valvular defect → valvular insufficiency → reflux);
- hypotheses incriminating arterio-venous anastomoses (opening of arterio-venous shunts → venous hypertension → valvular insufficiency → reflux).

These hypotheses can be considered unitarily, based on their hemodynamic consequences: all these mechanism lead to an overcharge in the superficial venous system, and, as a common result, in blood reflux. Reflux occurrence and development is progressive, initially in a horizontal manner (through perforating veins), later in a vertical manner (through superficial veins). During the first stage, a transfer of blood mass occurs, from the deep venous system (DVS) to the superficial venous system (SVS). During the next stage, the supplementary blood volume (the precharge) is circulated backwards, under the gravitational force, and generates venous hypertension within the epifascial venous system. According to the French phlebology school, the occurrence of primary varices is fundamentally linked to a vertical truncal reflux responsible for the passive dilatation of the distal superficial venous network. This concept is not accepted by the Anglo-Saxon school, where specific explanations are contradictory.

A series of arguments found in specialty literature, corroborated with personal clinical, echodoppler, phlebography, immunohistochemical, biological observations, sustained with physical and mathematical proof on venous hemodynamics, all demonstrate the pathophysiological “insufficiency” of the classic hypotheses.

1. The jet (“blow-out”) phenomenon was first described by Cockett in 1953, and often invoked by the Anglo-Saxon school to explain varicose ampullary dilatations at perforating veins level, cutaneous trophic lesions, ulcers and hypodermis plaques – all these are often encountered outside primary varices. Moreover, Schultz-Ehrenburg noted that, in 10-12 year old children born to varicose risk families, there are insufficient

perforating veins without signs of varicose transformation on the drained superficial veins. It is true, however, that years away, some of these children will become varicose disease patients (1). Segmental refluxes were encountered in both deep and superficial veins of the lower limbs, in otherwise healthy subjects (2). In the leg, considering only the median medial and posterior third and the distal medial third of the leg, on a group of 554 cases with chronic venous disease, Delis notes a 54.8% prevalence of perforating veins insufficiency. In other words, more than half of the cases with perforating veins insufficiency, covering the entire chronic varicose disease spectrum in the lower limbs (C0-C6), occur in the distal two thirds of the leg. These observations are not just statistical artefacts. They support our earlier observation according to which distal leg insufficient perforating veins, often isolated, represent an “escape gateway” for a distal transversal reflux that generates a certain type of primary varices (3). The veracity of this theory was verified in duplex colour monitoring of primary varices over long periods of time, 12-15 years, in specifically selected patients having professions predominantly static or requiring strenuous efforts in orthostatism, humid and warm environment, with no heredo-collateral antecedents for varicose disease or collagen pathology. Under these circumstances (constitutional venous hypotonia), when genetic determinism is highly improbable, an acquired venous hypotonia is not at all impossible, related or not to local dysplastic factors, and allowing non-diathetic primary varices to develop orthogradely (3). Arguments that support this hypothesis:

- hydrostatic (hemostatic) pressure is maximal within distal leg segments,
- dynamic or pump pressure, with its "pressure chamber" located in the proximal third of the leg, reaches a level of 200-250 mmHg during “systole”. Each contraction also generates hydraulic shocks in the distal axial valvular segments. These shock waves are transmitted axially and retrogradely, beneath the "pressure chamber", with the speed of sound, and, acting on dysplastic and fragilized veins, represents the determinant factor for distal axial valvular and perforating vein lesions, which function as real "admission canals" to the solear pressure chamber. The predominantly mechanical, baric valvular insufficiency opens distal reflux canals which later generate varices of the leg associated with proximally competent saphenous trunk and crossa (primary non-gravitational varices)(1,2,3).

2. Rose and Tibbs reason that the internal saphenous vein had a structure sufficiently strong to allow passive dilatation from refluxant blood mass (4,5). The use of the internal saphenous vein in arterial bypass grafts demonstrated no dilatation, even though blood pressure is significantly increased (4). Moreover, in time, an intimal hyperplasia develops, thus the vein segment becomes arterialised (4). Experimental studies, performed in vitro, proved that venous wall and valves resist non-physiological pressures of 2.5-3 atm. The saphenous graft or patch used in coronary surgery has a median breaking pressure of 2873 mmHg (3.78 atm), corresponding to a median diameter of 4.58 mm.

3. In venous endoscopy, the retrograde perfusion of washing fluid demonstrated healthy valves have extreme solidity; their resistance, conferred by their “sparrow nest” geometrical conformation, is definitely superior to that of the venous wall (6,7).

4. Phlebologic literature shows cases with congenital valvular incontinence or valvular agenesis, that don't necessarily develop varices (8).

5. Crossectomy of insufficient internal saphenous vein, crossa ligature, endoclipping or any other procedure that halts vertical reflux don't determine the disappearance of the varices up high, and don't prevent future varices.

6. Venous endoscopy discovered varices not originating in perforating veins (6,7). Blanchenmaison mentions dilated saphenous collaterals – macroscopically abnormal, varicose – but with no reflux at their level or in the saphenous trunks.

7. There are varicose recurrences following radical surgical interventions (crossectomy associated with saphenectomy), performed by the book. Varicose recurrences are more frequent and more complex in the leg compared to the thigh (8), although the hemostatic pressure column was previously eliminated by stripping; although perforating veins have been pulled out in the suprafascial segment. This argument has a major contesting impact on the classical theory according to which vertical blood reflux is absolutely necessary and sufficient to explain primary varices pathogenesis; this theory is still firmly defended by the French phlebology school. In other words, the absence of vertical reflux (manifested essentially through the gravitational force is synonymous to the absence of varices. Clinical and duplex colour observations indicate primary varices in the leg with no reflux along the deep axis, with no traumatic or thrombotic antecedents, associated with continent GSV crossa and/or trunk (3,6). The prevalence of primary reflux with competent saphenous trunks was 43% and the reflux of GSV calf tributaries was the most common in the study of Seidel et al (10).

8. Using endoscopy, Blanchemaison noted leg varices communicating with the deep venous network through a gemellar perforating vein or through an isolated superficial vein that communicated directly with the popliteal vein, with the superficial femoral vein or with the common femoral vein (6). There are islets of varices isolated and independent from the saphenous courses – the so-called extrasystemic varices – that occur previously, concomitantly or following the surgery of internal or external saphenous system varices (7). Frequently, extrasystemic varices occur postoperatively (following saphenous systems surgery) and are reported as varicose recurrences although they are generated outside surgery site, and the initial intervention most often does not intercept any pathogenic link to the territory where they occur. In other words, they are part of the primitive varicose disease, for which progression is the main, and abusively invoked, characteristic. Though some of extrasystemic varices following a surgical intervention are metavarices, not recurrences. Some of them might be triggered by a pressural transfer from the pelvic venous network.

9. Close clinical observation, verified with echodoppler and phlebography, is relevant to discovering varices along

the distal segments of tertiary, quaternary etc. SVS courses; some of truncal varices occur later and the more frequent in older varices (3,6,7). A Basel study (Survey II) noted that 5.2% of men and 3.2% of women had truncal varices, while 51.8% of men and 64.8% of women had reticular varices – in other words, dilated collateral veins, or telangiectasias. The follow-up Basel study (Survey III) indicated an increase in truncal varices incidence up to 20% in men and 16% in women (11); in other words, the varicose truncal transformation occurred later, and this argument sustains our opinions as well. Similar data are seen in a longitudinal Japanese study, on a selected group of women, where truncal varices were encountered in 10% of cases, 16% had non-truncal, isolated varices, 13% had reticular varices and 7% telangiectasias; summing things up, 29% of patients had non-truncal varices, versus 10% with truncal varices (12). Engelhorn notes an GSV reflux prevalence significantly higher in the leg compared to the thigh. The prevalence of simple or multiple segmental refluxes, not considering the femoral-saphenous junctional reflux, scored 53%, significantly higher than all the other reflux types summed up ($p < 0.001$) (13).

10. Reflux and varices along the saphenous courses were noted in 10-30% of cases without terminal valve insufficiency. Seidl et al. indicate a 43% prevalence of refluxes along large internal saphenous vein collaterals, with competent saphenous trunk (10). Other times, varices develop unilaterally, in a single internal saphenous system, although sapheno-femoral junction insufficiency is noted bilaterally (14,15).

11. Varices can develop next to competent valves and/or beneath a competent venous segment (14,16,17)

12. Based on clinical and echodoppler observations, it's safe to say that the (terminal) valve insufficiency theory is not satisfactory, since it does not cover primary varices completely (3,17).

A disturbed hemodynamics – a damaged vein wall and angiotissue unit

The most phlebologists would agree that:

- varices develop in sectors of increased hydrostatic (“hemostatic”) pressure (high static pressure induces low blood velocities, according to Bernoulli's formula: $P_t = P_s + rv^2/2$ - initially, varices develop in venous stasis sectors (increased hemostatic pressure);
- venous stasis is equivalent to endothelial hypoxia (18);
- in orthostatism, the maximal hydrostatic (hemostatic) pressure, in other words the maximal parietal-valvular stress (90 mmHg) is encountered in the venous segments most distal to the heart – i.e. the venous segments in the foot.
- the most significant stasis is located in the segment where the left heart's propulsion force is exhausted and where the right heart's aspiration force is inexistent (the venous segments most distal to the heart); on top of this, there is the highest static pressure determined by gravitation. Despite all these theses being accepted, the ultimate conclusion delivers a global concept: all the abovementioned factors together generate the sapheno-

femoral junction dilatation and insufficiency, obviously affecting the terminal valve as well, followed by secondary reflux. According to this view, pathogenic factors act at the junction between the proximal third and the distal two thirds of the heart-sole blood column; obviously, this is not the level of maximal pressural stress.

The venous territory with the highest risk for varices is that where the blood column pressure opposed to the heart reaches the highest values. It is known that the hydrostatic pressure (to be more precise, "hemostatic" pressure, because blood's specific weight is slightly different from water's specific weight) is calculated as the product between the height of the fluid column and the fluid's specific weight. This parameter, as calculated and noted experimentally, has the highest values in the foot, and not at inguinal level. As a consequence, the lowest flow velocities, the important venous stasis, the tendency to flux inversion addressed by venous valves, all off these are noted in the most distal segments of the inferior caval system. As delicate anatomical structures immersed in a fluid filled with metabolic waste and poor in oxygen, venous valves are the most exposed to and traumatized by pressural aggression, stasis and local turbulences (mechanical elements that determine conformational modifications on Ca^{2+} and K^+ channels). These represent mechanobiochemical events capable of altering information transmission and reception, enzymatic and metabolic processes involved in maintaining the homeostasis of venous wall structures. The widening of intercellular junctions discontinues the informational flux, decouples and fragments the electric and metabolic activity of the endothelial "syncytium", isolating it from central integrating neuroendocrine signals.

"Insulations" appear, with functional segmentation on several venous sectors where local metabolic reactivity becomes prevalent in time, skipping central neuroendocrine control. The contractile, effector component in smooth muscle cells (SMC) diminishes following the subendothelial migration of a cellular group that transforms into a secreting phenotype. In this way, the capacity of dynamic parietal response to gravitational stress diminishes. The compensatory increase in collagen synthesis cannot counterbalance the loss of elastic resistance. The newly synthesized collagen (type III collagen) does not retain the initial fibrillar structure, nor the spatial disposition, and it distorts the cellular-fibrillar-matriceal interrelations and continuity. The anarchically arranged collagen fibres dissect and "insulate" nest of contractile SMCs ("venous wall cirrhosis"). An innervation deficit is also possible, the high levels of tissular monoamine oxydase is a strong argument for local metabolic amplification against neuronal control (19). Certain authors identify similarities between varicose transformation and experimental denervation not in adrenal mechanisms alone, but also in local histological changes (20). The deterioration of the parietal muscular-elastic reinforcement, the valves destruction transforms superficial veins in a "pressure and blood mass volume reception spaces" under gravitation. A progressively greater quantity of blood is "absorbed" from the DVS into the SVS according to Laplace's law. An increase in venous pressure and

parietal tension is generated. Lacking a "splint" of tissular structures, superficial veins dilate and continue to rely on perforants and collaterals. Veno-venous shunts appear, recirculating stasic blood. The lateral "depressuring" of the leg pump's venous component induces a decrease of the effective ejection fraction, and an increase in residual volume. In the end, there is a clear deterioration of the muscular pressure-generating "engine", and venous hypertension becomes permanent.

At endothelial level, following stasis and venous hypertension, intercellular spaces widen, allowing water to escape; hydric conductivity amplifies 15 times in the presence of activated leukocytes (21). The hydric conductivity increase leads to water, electrolytes, proteic macromolecules, PMN, lymphocytes accumulating in the interstice. First, there is an increase in lymphatic drainage, but, most probably, the consecutive interstitial fluid changes (higher viscosity), extracellular matrix distortions induce an uptake and transportation insufficiency of the lymphatics, with secondary oedema. Blood reaching venous collaterals is more viscous, following the loss of suspension liquid for cellular elements. The haematocrit increase favours erythrocyte aggregation, amplifies viscosity and, implicitly, the total resistances to flow, stasis and leukocyte margination. Thus, all the conditions are met for a coupled activation, of both leukocytes and endothelium (non-laminary or transitional flow, tangent force reduction, circumferential force increase, the "unmasking" of endothelial receptors, the expression of adhesion molecules etc). During stasis, high concentrations of cytokines are noted (22) which, in time, issues segmental deteriorations of the valvular system along sectors with the greatest pressural stress. The defunctionalization of distal perforants is succeeded by an extension of venous hypertension to certain microcirculation sectors. Activated cellular elements present in the interstice (leukocytes, erythrocytes, fibroblasts), interstitial oedema, extracapillary protein level increase, distort the stereodistribution of intercellular matrix, which uptakes collagen synthesis enhancing cytokines. Blood and lymph networks rarefy. Blood capillaries elongate, dilate, become visible on the skin and later contort to a glomerular aspect. The dynamics of filling and evacuation is perturbed, the angiotissular unit is affected with subsequent lesions: sclerolypodermatosis, venous ulcers. The progression speed of angiotissular lesions is invertedly proportional to the functional capacity of the lymphatic system. In other words, a short veno-lymphatic feedback loop reduces all chances of functional compensation, leading to trophic changes

An appealing unitary model

The complete understanding of varicose disease pathogenesis remains stuck at hypotheses level. The classic model under Trendelenburg's medical authority, seems today, at least in part, inexact. Terminal valve insufficiency and crossa reflux constitute either the final sequence in the much larger process of SVS defunctionalizing, or a way of generating one type of primary varices, i.e. gravitational

varices. Until now, more theories have been issued, based on epidemiological, clinical, anatomical and biochemical data. However, no formal argument, sustained by fundamental scientific knowledge, proved sufficiently accurate to explain the pathophysiological mechanism that generates this frequently encountered disease. On the other hand, the vicious circle of hemodynamic disturbances and parietal-valvular structural changes is fairly well known, without understanding the essential cause-effect relation. Following the amplification of biological investigation possibilities, such as the cellular and molecular insight technologies, certain hypotheses and models were abandoned while others new surfaced. A model needs to be evaluated from many points of view: e.g. how much observation and measurements of accessible phenomena, how much informal judgement and how much convenience they are based upon. A model is the more convincing, and thus real, the more it corresponds to the daily clinical experience (23).

Forcing conveniences, a couple of years ago, we dared formulate a pathogenic model informally sustained by clinical and paraclinical monitoring data (phlebography, colour 3D and 4D echodoppler, venous endoscopy, immunohistochemistry)(3). In accordance with the previously enumerated arguments, our model explains the pathogenic mechanisms of primary varices, confirmed in a significant number of patients. Primary varices develop in the SVS, where blood mass volume transfers occur through reflux. In general, one of the two major reflux “gateways” is forced initially: the inguinal gateway (the SFJ) or the leg gateway (the perforating veins in the leg). Later on, one gateway (the reflux or the “escape” gateway) opens the other (the “re-entering” gateway), unidirectional in the beginning, which becomes swinging and closes an autonomous pathogenic circle. The blood mass transfer, as well as the dynamic pressure transfer, describes a progressively re-circulating loop (veno-venous shunt). The elongation direction is retrograde (Hach’s classification) or orthograde, when the leg gateway is opened first. In the first instance, the overcharge is taken over almost exclusively by a perforating vein; in the latter instance, the overcharge is distributed between the suprajacent perforating veins and the saphenous trunk. The greater compensating capacity seen with orthograde progression reflects in a slower defunctionalization of the saphenous trunk. Thus, primary varices can occur in two ways: a retrograde, descending way, classically described as being opened by the gravitational force, leading to gravitational varices; and an orthograde, ascending way, opened by pressure escaping from the calf muscular-venous pump following the deterioration of the “admission valves” to the “pressure chamber” – the perforating veins in the leg. This type of primary varices is non-gravitational. The specific leg geometry, the conformation and distribution of the calf muscles, the vascular cross-section differences at various levels in the leg, which correspond to inherent “pressure absorption” differences, expose to hydraulic shocks during sudden contractions predominantly Cockett III and Cockett II perforating veins. These perforating veins are located on leg segments with no muscular mass (low pressure

absorption) and, consequently, are short, oriented horizontally and have large calibre. Located between two pressure chambers, i.e. the plantar chamber, pushing blood orthogradely, and the leg chamber, pushing blood retrogradely as well, Cockett II and Cockett III perforating veins are “risk perforants”, possibly as risky as the inguinal “great perforant”. This is why they become insufficient so frequently. They also circumscribe “the ulcerogenic area of the leg”.

Primary varicose vein – classification and peculiarities

Depending on those pathogenic factors and progression of disease, we acknowledge the following subtypes of primary varices:

1. Varices associated with reflux:
 - diathetic, gravitational, retrograde primary varices;
 - non-diathetic, non-gravitational, pump, orthograde primary varices.

2. Varices not associated with reflux, “suspended varices”.

Gravitational primary varices have the following characteristics:

- occur on a constitutional hypotonic phlebopathy (diathetic background);
- the constitutional disposition of deep femoral vein (DFV) and GSV confluence orifices with the main venous axis facilitates the direct blood mass volume transfer from DFV in the GSV crossa during effort (e.g. Valsalva manoeuvre);
- occur on a prolonged orthostatic or desk activity;
- descending progression;
- primarily truncal morbidity;
- collaterals rarely affected;
- physiopathologically, a long loop recirculation phenomenon occurs;
- cutaneous trophic lesions occur late and are more attenuated;
- postsurgical recurrence is possible.

Non-gravitational or pump primary varices have the following characteristics:

- occur on an acquired hypotonic phlebopathy; often, patients don’t have heredocollateral antecedents for collagen pathology (hernias, hemorrhoids, CVD). Prolonged orthostatic activity, performed in warm environments, prolonged sports activity that issues sudden leg contractions (jumping, running, relay racing etc) are frequently encountered factors.
- predominantly orthograde progression, with continent SFJ.
- not necessarily truncal in the beginning, depending on the connection to the insufficient perforating vein; most of the extra- and intersystemic varices fall in this category.
- secondarily truncal morbidity.
- physiopathologically, a short loop re-entering or recirculation phenomenon occurs.

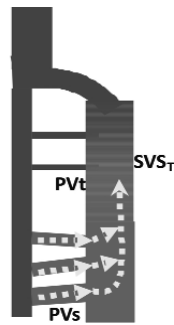


Figure 1. Orthograde development of varicose veins

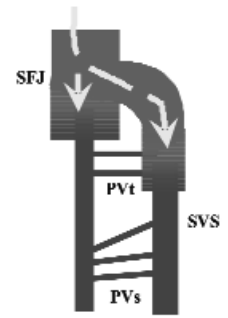


Figure 2. Retrograde development of varicose veins

- cutaneous trophic lesions and oedema occur earlier and more frequent.
 - postsurgical recurrence is highly improbable.
- “Suspended varices” show the following traits:
- usually occur along segmentally dysplastic venous courses;
 - no perforating vein can be identified showing pressure and blood mass volume transfer from the deep venous system;
 - are similar to venous angiomas;
 - don't recur postsurgery.

The therapeutic importance of this classification is evident.

To conclude, as far as current knowledge allows, primary varices pathogenesis, appears more complex and nuanced. Varicose transformation on venous courses can occur in a retrograde manner (*fig. 1*) (the classic and unilateral model for gravitational varices), in an orthograde manner (*fig. 2*) (non-gravitational, pump varices) or following blood stasis in limited, dysplastic segments (“suspended varices”). The therapeutic implications are obvious, and the results predictable.

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