Proximal long saphenous vein valves in primary venous insufficiency

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PROXIMAL LONG SAPHENOUS VEIN VALVES IN PRIMARY VENOUS INSUFFICIENCY

Histopathology and pathophysiological implications

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RÉSUMÉ :

Les valvules proximales de la veine grande saphène. Histopathologie et implications physiopathologiques.

Objectifs : Vérifier les données de la littérature sur la description des valvules veineuses et leurs éventuelles conséquences au plan physiopathologique et clinique.

Matériel et méthodes : Les différents éléments constituant les valvules proximales de 65 veines grandes saphènes ont bénéficié d'une étude anatomopathologique. Les échantillons examinés avaient été obtenus sur des veines grandes saphènes ayant été prélevés par exérèse chirurgicale chez des patients opérés de varices.

Les éléments morphologiques et les différentes mesures ont été évalués par microscopie optique.

Résultats : L'épaisseur du sinus valvulaire, l'implantation pariétale et la partie proximale de la valve varient de façon parallèle.

L'épaississement est lié à une augmentation du nombre des cellules musculaires lisses au niveau de l'insertion pariétale et à une dissociation des couches élastiques.

L'épaississement de la partie distale de la valve se fait aux dépens des éléments du collagène. Elle peut être raccourcie, plissée et son bord peut être épaissi.

La paroi veineuse au niveau d'un anévrysme commissural est en règle plus mince qu'au niveau du sinus valvulaire.

Des altérations de l'intima, de la membrane élastique et de la média ont éte identifiées dans 98 % des anneaux valvulaires. Les lésions ectasiques et asymétriques de la paroi veineuse sont essentiellement dues à une hypoplasie de la média.

Conclusion : Le développement d'une insuffisance veineuse primitive pourrait être lié à 2 facteurs constitutionnels: la dilatation de l'anneau valvulaire et l'hypotrophie valvulaire aggravées par l'impact traumatique d'origine hémodynamique sur ces lésions initiales. L'interprétation au plan physiopathologique de l'insuffisance veineuse impose un diagnostic détaillé avant d'entreprendre une réparation valvulaire chirurgicale. (J Mal Vasc 2000 ; 25 : 27-36)

Mots-clés : Valvule veineuse. Insuffisance veineuse. Veine saphène. Varices.

ABSTRACT :

Proximal long saphenous vein valves in primary venous insufficiency. histopathology and pathophysiological implications.

Objective : To verify some of the previous findings of venous valves described in the literature, their pathophysiological significance and clinical implications.

Materials and methods : The elementary components of 65 proximal valves of the long saphenous vein and their interrelationships were subjected to histopathological examination. Valves were taken from patients subjected to long saphenous vein surgical removal for varicose veins of the lower limbs.

Measurements and morphological evaluations were performed by optical microscopy.

Results : The valvular sinus, agger and proximal portion of the cusp underwent parallel variations of thickness.

Thickening of the proximal portion of cusp was related to increase in smooth muscle cells in the agger and to elastic layer dissociation.

Thickening of the distal portion of cusp depended on the collagen component; sometimes it was shortened, crumpled and led to the formation of a thickened border. The vein wall in a commissural aneurysm was usually thinner than in the valvular sinus. Alterations in the intima, in the elastic membrane and in the media were found in the 98% of the valvular annulus. Ectasis and asymmetry of the venous wall were mainly related to the muscular hypoplasia of the media.

Conclusions : The development of primary venous insufficiency seems to be due to the following tissue alterations: dilatation of the valvular annulus and hypotrophy of the cusp. The hemodynamic mechanical injury increases the tissue damages of both annulus and cusps. This pathophysiologic interpretation of venous insufficiency suggests the need for detailed diagnostic procedures before reparative surgery of valves. (J Mal Vasc 2000; 25: 27-36)

Key-words : Venous valves. Venous insufficiency. Saphenous vein. Varicose veins.

From the beginning of this century up through the past 10 years several authors (Kampmeier 1927 — Edwards 1940 — Basmajan 1952 — Cotton 1961 — Haeger 1978 — Watts 1978 — Leu 1985 — Van Bemmelen 1986 — Rose 1986 — Zelikowski 1986 — Gottlob, May 1986 — Obitzu 1990 — Rose, Butterworth 1992) developed the theory of "primary vein wall dilatation" in order to explain the development of primary venous insufficiency. Wall dilatation is supposed to be followed by cusp degeneration in the more advanced disease (1, 2).

On these bases other authors developed and performed various techniques for surgical valve repair in deep veins (Psatakis, 1964; Hallberg, 1972; Kistner, 1980-90; Queral, 1981; Raju, 1985; Taheri, 1985; Lane and Jessup, 1986; Camilli, 1987; Sottiurai, 1990; Perrin, 1992; Welch, 1992; Simkin, 1992; O'Donnell, 1993; Belcaro, 1993) and in superficial veins (Hallberg, 1972; Lane, 1986; Jessup-Lane, 1988; Camilli, 1988; Corcos, 1989; Zamboni, 1990; Gasbarro, 1990; Donini, 1991; Atzeri, 1991; Partsch, 1992; D'Agata, 1992; Hetenyi, 1992; Hoshino, 1992; Lane, 1994; Schanzer, 1994; Vedensky, 1994) (1, 2).

At follow-up excellent and stable results were obtained in a large number of patients, however some discrepancies with the basic pathophysiologic concept were observed.

At the same time other authors proposed the theory of "primary valve degeneration" (3, 4) but this explanation proved unsatisfactory in detecting a primary factor for disease onset and development.

A recent retrospective study performed in 72 patients with sapheno-femoral junction insufficiency undergoing external valvuloplasty demonstrated that the best results could be obtained in cases with early disease. Indeed 18% of the early cases developed postoperative recurrent reflux while 50% of the cases with advanced disease showed no recurrent reflux. The conclusions were that in 18% of the early cases the valvular cusps were already damaged and in 50% of the late ones the cusps still had normal structure and function (1, 2). These observations appeared to be in contrast with the previous theories and raised some doubts about the anatomical pathophysiology of primary venous disease.

A review of the literature on venous valve morphology (5-10) was performed to seek an explanation of these clinical findings and their pathophysiological implications.

Different parts and surfaces of cusps were taken into consideration in the literature (5-10): the agger, the parietal and luminal parts of the leaflet, as well as the proximal and distal portions and border.

The main alterations described in the agger of degenerated cusps were the increase in smooth muscular and connective tissue cells often surrounding the vasa vasorum. Intimal plaques were frequently observed below the agger (endo-phlebo-hypertrophy). The leaflet variations were more often represented by irregular thinning or thickening, elastic membrane fragmentation and dissociation and fibroblast proliferation. The surface of the leaflet luminal part was relatively smooth, whereas the parietal was irregularly outlined by segmentary thickness reductions covered by the endothelium named "crypts"; they appeared to be arranged in an irregular manner and occasionally absent (9). Cyst-like structures containing erythrocytes beneath the leaflet endothelium were observed in some cases. The free borders were sometimes thickened.

However, the development of the tissue alterations in the valve cusps and the leaflet thickness were not found to be constant: some normal cusps were observed in dilated veins and, in some others, pathologic cusps were found in undilated valvular annulus. Sometimes the cusps appeared to be tortuous and prolapsed.

Post-thrombotic-like alterations were found in subterminal valves of long saphenous varicose veins as cusp retractions, cusp and venous wall adhesion, commissure dilatation and various endothelial alterations. The latter observations led several authors (6) to develop the theory of post-thrombotic valvular destruction.

Venous wall dilatation was observed in the valvular annulus in 11/21 cases studied by previous authors (6) and a venous aneurysm in 5/21. Thick intimal plaques were frequently observed below the valvular cusps and the dilated commissures (endo-phlebo-hypertrophy) which often were found to be aneurysmatic. Inflammation of venous valves in cases affected with acute endocarditis, chronic rheumatoid disease and thrombosis of valvular pockets were also described (6, 7, 10).

A first verification was done in our departments by clinical, echographic, angioscopic and histopathologic studies on 42 sapheno-femoral valves examined after surgical removal of varicose veins of the lower limbs (11). The following data emerged.

- Thinning of leaflets was the prevalent alteration observed in the cusps.
- Dilatation, ectasis and asymmetry of the vein wall were the prevalent annulus alterations.
- No relationship was found between parietal ectasis and cusp alterations.
- In some cases hypotrophic cusps and normal annulus and in some other normal cusps and dilated annulus were observed.

Primary venous wall dilatation was detected in the valvular annulus in only 21.4% of the histological samples, in 30,9% of cases vein wall dilatation was combined with cusp hypotrophy and in 5/6 incompetent sapheno-femoral valves, explanted for recurrent reflux after external valvuloplasty, the cusps disappeared (3 cases) or were extremely thinned by hypotrophy (2 cases).

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The statistical analysis was performed by the Statistical Dept. of the Crinos Pharmaceutical Products, Italy.

The conclusion of the study was that in the majority of the cases primary annulus dilatation and some early hypotrophic cusp damage can develop simultaneously. For this reason the two theories of vein wall dilatation and primary degeneration of the cusp seemed to overlap in the majority of the cases.

The aims of the study were to detect the relationships between the elementary alterations of the venous wall and of the cusps, to define the concept of cusp hypotrophy, its clinical significance and to clarify the pathophysiology of primary venous insufficiency in order to perform a more detailed diagnostic assessment of venous valves before reconstructive surgery.

MATERIALS AND METHODS

During the previous studies (12) elementary histologic alterations were found in the 11% of the venous segments taken from patients without evidence of venous disease. This makes extremely difficult to perform a comparison between pathologic venous structures and normal ones.

The macroscopic observations of varicose veins removed by surgery led us to the conclusion that the measurements of vein diameter, cusp and venous wall thickness vary from subject to subject. This variation seems to depend mainly on vein size.

Primary importance was given to the following measurements. The valvular sinus thickness was evaluated above the cusp insertion in the longitudinal sections *(fig. 1, 2)* and in the cross sections approximately in correspondence with the valvular pocket middle portion. The valve agger thickness measurement was performed close to the annulus wall and the proximal part of the leaflet at the middle third.

The clinical-anatomical characteristics of the patients and histologic techniques employed are summarized in *table I.* 17 longitudinal and 48 cross (two of them were oblique) sections of proximal saphenous valves were studied.

The protocol of the microscopic evaluation are summarized in *table II.* The anatomical and histological details subjected to microscopic evaluation are schematically described in *fig. 1a-1b.*

STATISTICAL ANALYSIS

Quantitative variables were expressed as mean values and standard error. The results were examined by analysis of variance. Correlation analyses were examined with Pearson's correlation. Qualitative variables were expressed as frequencies and percentages. The chi square test of independence was used when the values were sufficiently large, otherwise Fisher's exact test was used.

The following correlations were analyzed:

— thickness: agger/valvular sinus;
— thickness: agger/leaflet proximal part and distal part;
— thickness: valvular sinus/leaflet proximal part;
— thickness: agger — leaflet/leaflet morphology;
— thickness: agger — leaflet/elementary histologic alterations;
— thickness: border/leaflet;
— thickness: border/commissural aneurysm;
— ectasis-asymmetry of the vein wall/muscular hypoplasia;
— ectasis-asymmetry of the vein wall/muscular hyperplasia;
— thickness of the vein wall/elementary histologic alterations;
— thickened border/fibro-muscular plaques below the valve.

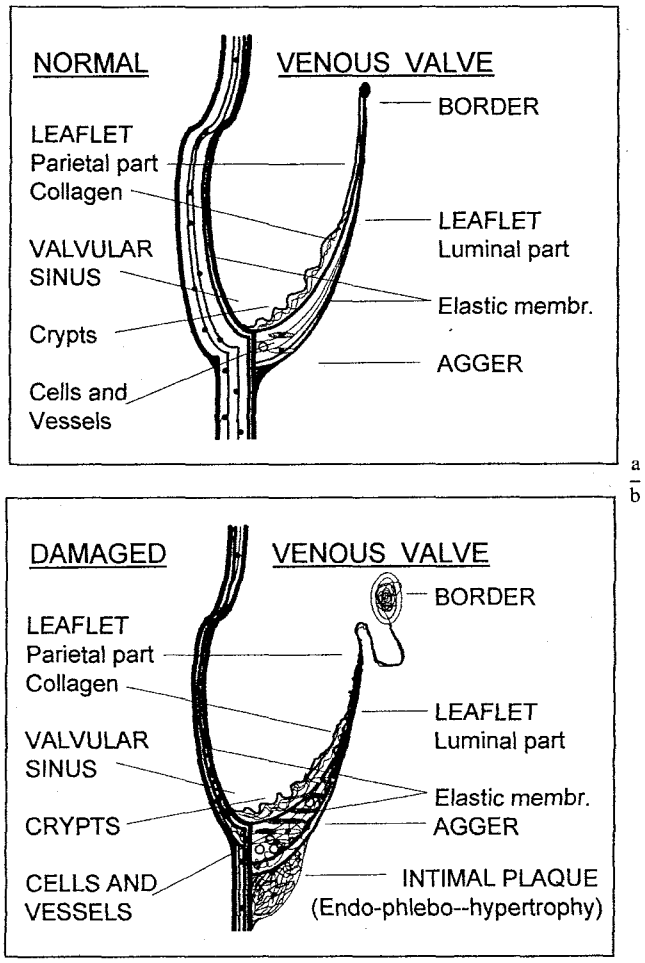

FIG. 1. – a) Schematic example of a long saphenous vein proximal valve in a longitudinal section. The valvular apparatus appears to be free from elementary tissue alterations as it would be in normal conditions. The different valvular parts and the anatomical-histological components studied are shown. b) This example of a damaged valve summarizes the main alterations observed: thinning of the venous wall and distal portion of the leaflet, where the border is often crumpled and thickened; thickened agger with increased number of cells and vessels; elastic membrane fragmentation and dissociation; flattened crypts; endo-phlebo-hypertrophy below the valve agger. The more frequent and significant combinations of these elementary tissue alterations are described and analyzed in the text.
a) Exemple schématique d'une valvule de la veine grande saphène proximale et coupe longitudinale. L'appareil valvulaire est exempt de toute altération tissulaire comme il devrait se présenter dans des conditions normales. Les différentes portions valvulaires ainsi que les composantes histologiques et anatomiques étudiées sont indiquées b) Dans cet exemple concernant une valvule pathologique, les principales altérations observées sont présentes : amincissement de la paroi veineuse qui constitue l'anneau valvulaire et de la portion distale du lambeau au niveau de laquelle le bord paraît souvent recroquevillé et épaissi ; base valvulaire épaissie avec augmentation des cellules et des vaisseaux ; morcellement et dissociation de la lame élastique interne ; cryptes aplaties sur la partie distale du lambeau et endophlébohypertrophie en dessous de l'attache valvulaire. Les combinaisons les plus fréquentes de ces altérations sont décrites dans le texte.

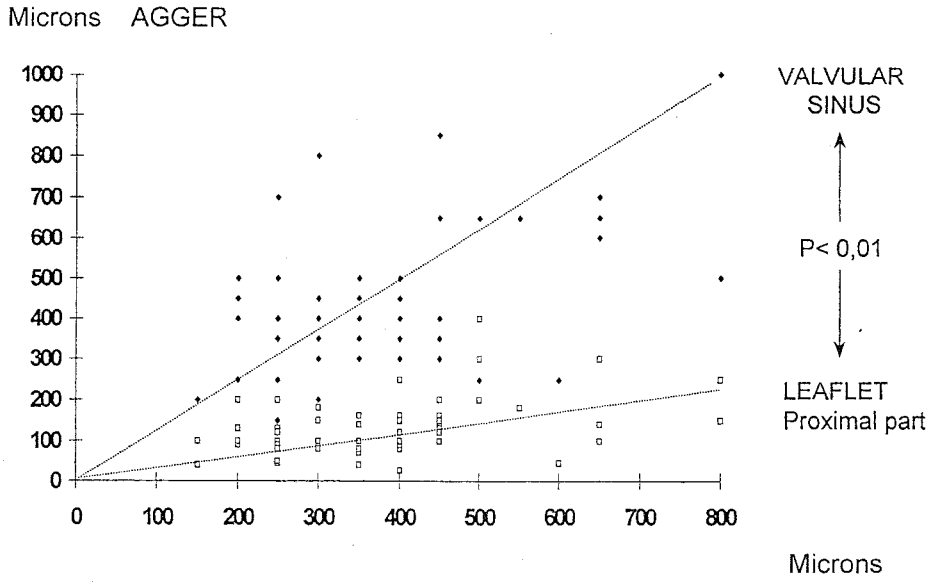

FIG. 2. – Cusp agger, proximal part of the leaflet and evaluation and comparison of valvular sinus thickness. Comparison between cusp agger and valvular sinus thickness: ● P < 0.001. Comparison between cusp agger and leaflet proximal part thickness □ P < 0.001. Comparison between leaflet proximal part and valvular sinus thickness ● ↔ □ P < 0.01. Due to the thickness of the three structures they seem to overlap and undergo parallel variations.

Comparaison entre les mesures en microns des épaisseurs de la base, du lambeau proximal et du sinus valvulaire. Base/sinus ● P < 0,001. Base/lambeau proximal □ P < 0,001. Lambeau proximal/sinus ● ↔ □ P < 0,01. L'épaisseur de ces trois structures semble varier parallèlement.

RESULTS

NON SIGNIFICANT CORRELATIONS *(TABLE III)*

The number of connective tissue cells and vasa vasorum in the cusp was variable and did not appear to be related to the cusp thickness; no relationship was found between the thickness of the leaflet and the collagen component in the luminal part.

The crypts in the proximal part of the leaflet part were of a variable depth, while they usually appeared to be flattened or absent in the distal portion of thinned leaflets (P = 0.075).

TABLE I. – Histopathological examination of 65 proximal long saphenous vein valves. clinical-anatomical characteristics and histologic techniques.

Examen histopathologique de 65 valvules proximales de la grande saphène. Caractéristiques clinico-anatomiques et techniques histologiques.

Pathology	Varicose veins of the L.L. 65 cases
Sex	Males 18, Females 47
Age of Patients	Min.33, Max. 84, Mean 56,7 s.c. 1.66
Age of Disease	Min.3, Max. 40, Mean 20.0 s.c. 1.17
Valves	Terminal 9, Subterminal 45, Indeterminate 11
Stain	Hematoxilin-Eosin, Weigert, Van Gieson
Sections	Cross 46, Longitudinal 17, Oblique 2

The border was observed in 32/65 cases studied and it appeared to be thickened in 23 (71.8%). No relationship was found between the thickening of the border and the commissural dilatation or aneurysm or with the presence of intimal fibro-muscular plaques below the cusp insertions. The intimal plaques (endo-phlebo-hypertrophy) in the annulus below the valve were observed in only 4/15 longitudinal sections and in 8/43 cross sections (total 21.4%).

The commissures could be studied in 43 of the 46 cross sections. In 3 cases they could not be clearly seen owing to technical artifacts. Out of 32 cases (74.4%) the dilatation or aneurysm of one commissure (7 cases) and of both commissures (25 cases) was found. In 11 cases (25.5%) both commissures were normal. None of the elementary alterations observed in the commissural wall were found to be related to the valvular annulus dilatation.

Some inflammatory cells were detected in the valve tissues of six cases with thrombotic occlusion. The valve cusps were not severely damaged in four cases with early thrombosis. No inflammatory cells or microthrombi were observed in any of the other cases.

SIGNIFICANT CORRELATIONS *(TABLE IV)*

The mean thickness values of the valve agger (378.226 microns) were close to those of the valvular sinus (409.841 microns), measured in correspondence of its thinnest part, (P < 0.001) and a good relationship was found between the mean agger thickness and the thickness

TABLEAU II. – Histopathological examination of 65 proximal long saphenous vein valves parameters examined and the study protocol.
Examen histopathologique de 65 valvules proximales de la grande saphène : paramètres examinés et protocole d'étude.

ANATOMICAL PART		COMPONENTS	MEASURES AND GRADING
Cusp	AGGER	Thickness: max. min,	Microns
		Smooth muscular cells	0 = none; 1 = some isolated cells; 2 = spaces between cells; 3 = full.
		Fibroblasts	0 = none; 1 = some isolated cells; 2 = spaces between cells; 3 = full.
		Vessels	0 = none; 1 = one; 2 = some; 3 = numerous.
	LEAFLET (Proximal distal)	Thickness: max. min.	Microns
		Thickened-Thinned-Normal	Morphologic evaluation
		Smooth muscular cells	0 = none; 1 = some isolated cells; 2 = spaces between cells; 3 = full.
		Elastic membrane fragmentation-dissociation	0 = normal; 1 = rare duplications; 2 = extensive dissociation; 3 = dissolvement
		Collagen parietal part	0 = absent; 1 = elastic membrane thickness; 2 = elastic membrane thickness.X 2; 3 = elastic membrane thickness > X 2.
		Collagen luminal part	
		Crypts: normal, deeper, flatter	Morphologic evaluation
	BORDER	Normal, thickened, thinned	Morphologic evaluation
Annulus	SINUS	Thickness	Microns
	WALL	Ectasis-Asymmetry	Yes — No
		Muscular hyperplasia	Yes — No
		Muscular hypoplasia	Yes — No
		Sclerosis of the media	Yes — No
		Elastic membrane fragment	Yes — No
		Intimal plaques below V.	0 = none; 1 = 1/3 vein wall; 2 = 1/2 vein wall; 3 = Vein wall.
Special findings		Thrombosis	Description
		Thrombotic sequelae	
		Tributary veins with valves	
		Endothelial cysts	
Commissure	1 – 2	Aneurysm or dilatation	Yes — No
		Thickness (max-min-mean)	Microns
		Elastic membrane fragment.	0 = normal; 1 = rare duplications; 2 = extensive dissociation; 3 = dissolvement
		Intimal plaques (endo-phlebo-hypertrophy)	0 = none; 1 = 1/3 vein wall; 2 = 1/2 vein wall; 3 = Vein wall.

of the proximal part of the leaflet (mean thickness = 133.175 microns) ($P < 0.05$). The comparison between values for the valvular sinus and the proximal part of the leaflet was also significant ($P < 0.01$) *(fig. 2)*.

The optical microscopic morphologic evaluation of the thickness of the leaflet's distal part was compared to its size expressed in microns. There was a significant difference between the thickened leaflets (mean thickness = 133.175 microns) and the thinned ones (mean thickness = 19.762 microns) ($p < 0.05$).

However the thickening of the whole leaflet appeared to be mainly related to the collagen grade 2 thickness in the parietal part ($P < 0.001$) *(fig. 3)*.

No relationship was found between the elementary cusp alterations and other parameters. However some significant results ($P < 0.05$) were obtained from the observation of the number of smooth muscular cells in the agger which increases up to grade 2 in the thickened proximal part of the leaflet *(fig. 4)*.

A grade 2 fragmentation-dissociation of the elastic membrane was found in the proximal part of thickened

TABLEAU III. – Histopathological examination of 65 proximal long saphenous vein valves: non significant correlations.

Examen histopathologique de 65 valvules proximales de la grande saphène : corrélations non significatives.

ELEMENTARY ALTERATIONS AND ANATOMICAL COMPONENTS OBSERVED	St. an.
Thickness of leaflet (microns)/cells, vessels, collagen of the luminal part (morphology)	n.s.
Thickness of hypotrophic leaflet distal part (microns)/flattened crypts (morphology)	n.s.
Commissural aneurysm or dilatation/thickened border/intimal plaques (morphology)	n.s.
Commissural wall elementary alterations (morphology)/annulus dilatation (morphology)	n.s.
Inflammatory cells — none	not analyzed

leaflets in the majority of the samples ($P < 0.05$). In some of them the elastic fibrils occupied the whole thickness of the parietal part of the leaflet and of the free border *(fig. 5)*.

A thickened border was observed more often in leaflets with an apparently thickened distal part ($P < 0,05$) *(fig. 3)*. The objective observation of the border, especially by Weigert stain, demonstrated that it may represent the result of retraction and crumpling of the thinned hypotrophic distal part of the leaflet *(fig. 6, 7)*. At the latest stage of the crumpling process the border appears to be thickened and only the proximal part of the leaflet can be observed *(fig. 7)*.

Finally, the examination of the vein wall in the valvular sinus and commissure demonstrated that the ectasis-asymmetry are mainly due to muscular hypoplasia ($P < 0.001$) and that the commissural aneurysm, when present, (mean thickness= 219.968 microns) can become the thinner part of the ectasic anulus (mean thickness of the valvular sinus = 409.841 microns) ($P< 0.001$) *(fig. 8)*.

Sclerosis of the media, elastic membrane fragmentation-dissociation and intimal fibro-muscular hypertrophy with plaques, were found in 97% of the vein walls examined *(fig. 8)*.

DISCUSSION

The valvular sinus and the valve agger are approximately of similar thickness in the same subject. The thickness of the proximal part of the leaflet undergoes parallel variations. In other words the tendency of these structures to become thicker or thinner seems to be related. On the other hand early or late cusp degeneration was seldom observed and this confirms the overlapping of the two main pathophysiologic theories of primary venous disease: the first based on the primary vein wall dilatation and the second on primary cusp degeneration.

In previous studies some hypotrophic damage was observed both in the annulus and cusp of many cases. For

TABLEAU IV. – Histopathological examination of 65 proximal long saphenous vein valves: significant correlations.

Examen histopathologique de 65 valvules proximales de la grande saphène : corrélations significatives.

MEASUREMENTS AND ANATOMICAL COMPONENTS COMPARED	St.an.
Thickness of: valvular sinus (microns)/agger (microns)/proximal portion of cusp (microns)	$P < 0.001$
Thickened distal portion of cusp (microns) > thinned (microns)	$P < 0.05$
" (microns)/thickened border (morphology)	$P < 0.05$
" (microns)/collagen increased (morphology)	$P < 0.001$
Thickened proximal portion of cusp (microns)/smooth muscle cells in the agger (morphology)	$P < 0.05$
" (microns)/elastic layer dissociation (morphology)	$P < 0.05$
Commissural aneurysm mean thickness (microns) < valvular sinus mean, thickness (microns)	$P < 0.001$
Intimal plaques, elastic dissociation, sclerosis of the media in > 98 % valvular annulus (morphology)	$P < 0.001$
Ectasis-asymmetry of the valvular annulus/muscular hypoplasia (morphology)	$P < 0.001$

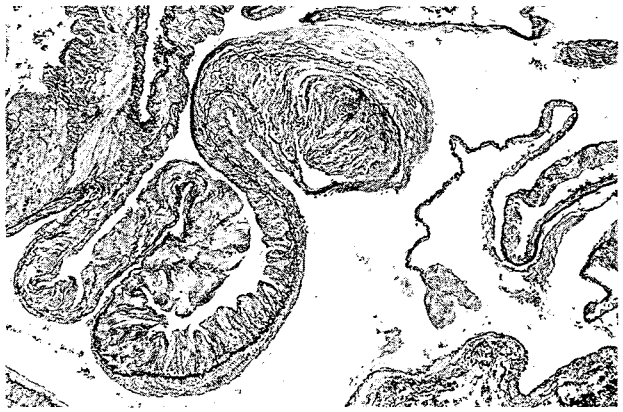

FIG. 3. – Low cross section of a proximal valve. Two opposite cusps are visible: one is thickened and the opposite one is thinned. The main difference is represented by the collagen thickness in the parietal part of the leaflet. The two borders are thickened. A whirled architecture is visible in the larger one. Weigert 150 X.

Coupe transversale basse d'une valvule proximale. Deux cuspides opposées sont visibles : l'une épaissie et l'autre amincie. La différence principale réside dans l'épaisseur du collagène sur le versant pariétal du lambeau. Les deux bords sont épaissis. Sur le plus grand des deux, on peut voir une architecture en tourbillon (vortex). Weigert 150 X.

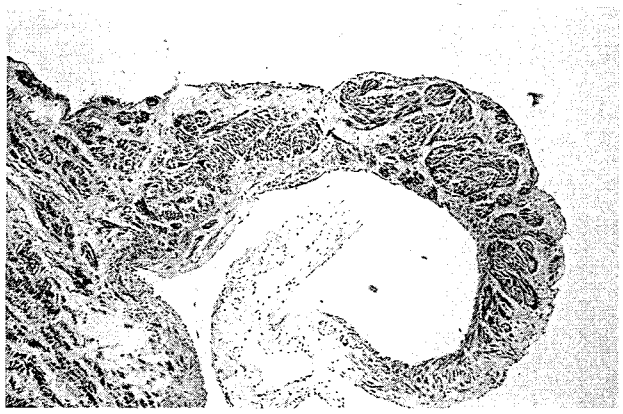

FIG. 4. – Longitudinal section of a prolapsed proximal valve. The agger and the proximal part of the leaflet are thickened by the presence of smooth muscular cell bundles.Hematoxilin-eosin125 X.

Coupe longitudinale d'une valvule proximale en prolapsus. La base et la portion proximale du lambeau sont épaissies à cause de la présence de faisceaux de cellules musculaires lisses. Hématoxilin-éosin 125 X.

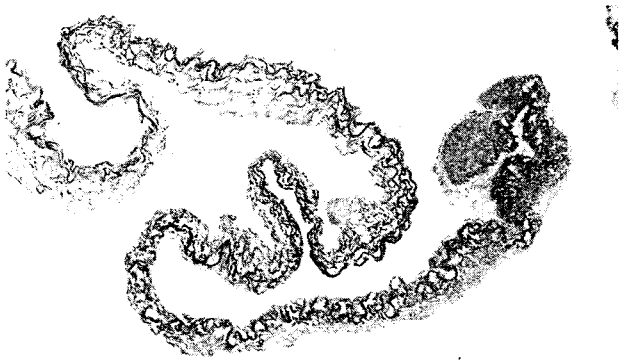

FIG. 5. – Cross section of a proximal valve. A 3 degree elastic membrane fragmentation and dissociation in the whole leaflet and in the border are present with the elastic fibrils spreading throughout the thickness of the leaflet. Weigert 300 X.

Coupe transversale d'une valvule proximale. Sur tout le lambeau et sur le bord épaissi, on peut voir le morcellement et la dissociation de la lame élastique interne au 3e degré avec fibrilles élastiques qui envahissent toute l'épaisseur du lambeau. Weigert 300 X.

FIG. 6. – Longitudinal section of a terminal valve. The proximal part of the leaflet is thickened by increased collagen in the parietal side. The distal part is thinned and the elastic membrane appears to be crumpled close to the end of the leaflet and in the border. A thick fibro-muscular plaque below the agger is visible. Weigert 125 X.

Coupe longitudinale d'une valvule terminale de la saphène proximale. La portion proximale du lambeau paraît épaissie à cause de l'augmentation de la composante collagène sur le versant pariétal. La portion distale est extrêmement amincie et la lame élastique interne recroquevillée au niveau de la fin du lambeau et sur le bord. Weigert 125 X.

this reason a more precise definition of hypotrophy becomes a matter of great interest (11).

Cusp thinning was mainly observed in the distal part of the leaflet and was usually represented by the reduction of the collagen and striking thinning to a minimum of 3 microns. These changes can be considered the expression of hypotrophy.

The literature (5-8) indicates that the increase of the vasa vasorum, connective tissue cells, smooth muscular cells and elastic fibers are usually present in the agger and leaflet of degenerated cusps. The results of this study demonstrated that they can sometimes be observed but, except for the smooth muscular cells and the elastic membrane alterations, they seem to represent mainly a structural variation rather than the expression of the valvular pathology.

Inflammatory cells were found only in the six cases affected with recent or previous thrombophlebitis and none in the primary valvular lesions. In the latter no microthrombi were found in the valvular sinus. These

FIG. 7. – Cross section of a proximal valve. The elastic membrane in the thickened border is crumpled in a spiral. The thickened border is the latest result of the crumpling of the distal part of the leaflet. Weigert 150 X.

Coupe transversale d'une valvule proximale. La lame élastique interne du bord est recroquevillée en spirale. Le bord épaissi semble représenter le résultat final du recroquevillement de la portion distale du lambeau. Weigert 150 X.

findings do not confirm the pathogenic theory based on post-thrombotic alterations. On the other hand the increased number of smooth muscular cells and the elastic membrane fragmentation and dissociation in the agger and in the proximal part of the leaflet appeared to be related to its thickening. No cellular proliferation was observed in the distal part of the leaflet which appeared to be thinned (hypotrophic) in the majority of the degenerated cusps.

The tickness variations of the leaflet's proximal part in correspondence with the crypts and their tendency to become flatter or disappear in the leaflet's distal part were

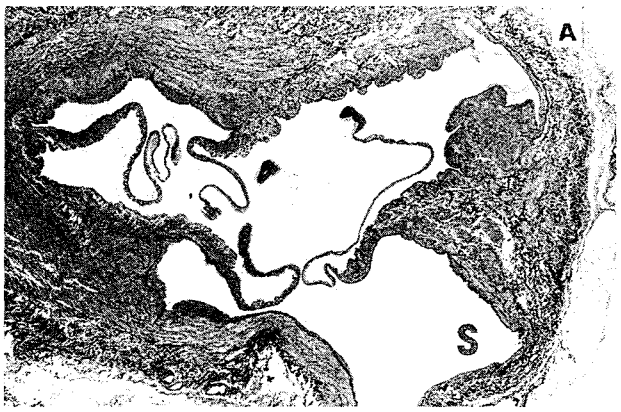

FIG. 8. – Cross section of a proximal valve. Sclerosis of the media, ectasis and asymmetry of the wall, fibro-muscular hypertrophy of the intimal layer. The minimum thickness in the commissural aneurysm (A) is less than in the valvular sinus (S). Weigert 15 X.

Coupe transversale d'une valvule proximale. Sclérose de la média, ectasie et asymétrie de la paroi, hyperplasie fibro-musculaire (endophlébohypertrophie) de l'intima, l'épaisseur minimum de la paroi dans l'anévrisme commissural (A) est plus faible que celle du sinus valvulaire (S). Weigert 15 X.

not significant and could not be taken into consideration for a further explanation of the primary venous pathophysiology.

The only elementary alterations that were found to be significant for this purpose are thus limited to the following:

- the number of smooth muscular cells in the agger and in the proximal part of the leaflet;
- the fragmentation and dissociation of the elastic membrane in the agger and in the proximal part of the leaflet;
- the thickness of the collagen in the distal part of the leaflet.

The problem of the significance of the thickened free border was often discussed in the previous literature but without reaching a satisfactory conclusion (5-9).

A good relationship was found between the thickened borders and the thickened distal parts of the leaflet but the more detailed observation of the thickened borders indicated that they are composed of crumpled distal leaflets. This probably means that the proximal part is the only visible portion, while the thinned one is crumpled and transformed in a thickened border. This transformation seems to be explained by the existence of some mechanical factors which should be mainly represented by the turbulence and cusp abnormal mobility due to the valvular reflux.

The intimal fibro-muscular plaques (endo-phlebo-hypertrophy) were easily detected in the longitudinal sections and by the observation of the intimal hyperplasia adjacent to the valvular agger in the cross sections as well *(fig. 6-8)*. However, the importance that the literature attributed to this alteration (5-8, 13) could not be confirmed by the observations coming from this study nor can they be considered as one of the specific expressions of primary valvular alterations. Their presence could also be explained by the annulus response to the chronic mobility alterations of the cusp but they did not appear to be related to other mechanical damages such as border thickening. However, it must be said that the intimal fibro-muscular plaques (endo-phlebo-hypertrophy) observed in several varicose samples previously studied (12) seldom appeared to be as thick as the ones observed below the valve cusps. For this reason it can be supposed that these findings may be due to a combination of biochemical and mechanical factors depending on the venous stasis caused by the reflux and its turbulence (13).

Sclerosis of the media, elastic membrane fragmentation-dissociation and intimal fibro-muscular hypertrophy with plaques, were present in the vein wall in almost all cases but muscular hypoplasia was found to be prevalent in the ectasic and asymmetric valvular annulus.

Both commissures were seen to be dilated more frequently than one alone and aneurysms were more frequent than simple dilatations. For this reason symmetric dilatation of the valvular annulus seems to prevail in the pathologic sapheno-femoral valves of varicose subjects.

The thinnest part in the annulus was not found to be located in the valvular sinus above the valvular insertion as the literature indicated but in the commissural aneurysm, when present.

PATHOPHYSIOLOGIC INTERPRETATION FOR PRIMARY VENOUS INSUFFICIENCY BY HISTOPATHOLOGIC STUDY OF 65 VENOUS VALVES.

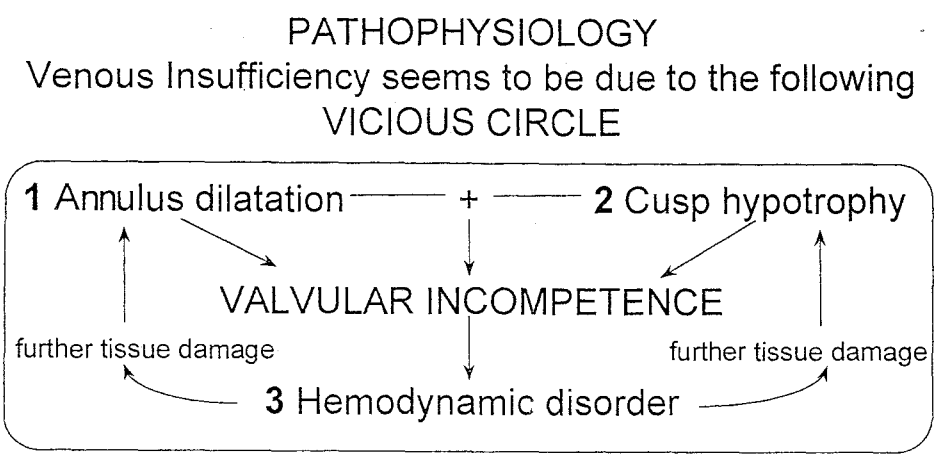

FIG. 9. – Three factors seem to concur in the onset and development of primary venous insufficiency: (1) annulus dilatation with hypotrophic parts, (2) cusp hypotrophy, (3) hemodynamic disorder which leads to mechanical injury of both annulus and cusps. One of the three factors can represent the beginning of the vicious circle which leads to venous insufficiency. In the majority of the cases studied they seem to overlap.

Il semble que trois facteurs concourent à déterminer l'apparition et l'évolution de l'insuffisance veineuse primaire : 1 - la dilatation de l'anneau valvulaire avec zones d'hypotrophie pariétale ; 2 - l'hypotrophie des cuspides ; 3 - le traumatisme mécanique sur la paroi et sur les cuspides causé par le trouble hémodynamique. Un seul des trois facteurs peut entraîner l'apparition du cercle vicieux qui provoque l'insuffisance veineuse primaire.

In one third of the cases the commissures were not dilated. In these subjects the valvular incompetence was probably due to primary hypotrophic cusp degeneration.

The histologic elementary alterations observed in the valvular components play a primary role in the preoperative evaluation before any kind of surgical repair of incompetent venous valves. The clinical outcome may be considered strictly related to the preoperative valvular conditions and can furnish the explanation of some recurrent reflux following reconstructive surgery of venous valves. For this reason a preoperative diagnostic assessment of these valvular conditions seems to be essential for establishing the proper indications for surgery. High resolution ultrasound examination and/or intraoperative angioscopy (1, 2, 11) would be satisfactory approaches to the problem and give enough informations in order to make the best technical choice.

CONCLUSIONS

The concept of valvular hypotrophy seems to emerge from the prevalence of the thinning of structures such as the distal part of the leaflet, the valvular sinus and the commissural aneurysm. Hypotrophy of these structures is mainly due to reduction of the collagen component in the leaflet and to media smooth muscular tissue hypoplasia of the valvular annulus.

The other main structural alterations related to the disease are represented by the increase of smooth muscular cells in the thickened leaflets and elastic membrane fragmentation.

The thickness of the cusp and annulus undergo the same variations in the majority of cases while the distal part of the leaflet sometimes becomes so thin and weak that it may bend, crumple and develop a thickened border. These alterations seem to depend mainly on the turbulence caused by reflux and thinned cusp flattening.

On the other hand it can be supposed that intimal fibro-muscular hypertrophy and thickening below the valve correspond to the response to blood stasis and hypoxia (13). However these endo-phlebo-hypertrophic plaques need not be considered a constant characteristic of primary venous disease but simply a consequence of reflux that may occur in some cases.

The histologic study of sapheno-femoral valves was able to detect tissue changes due to three pathophysiologic factors: primary wall dilatation, cusp tissue alterations and structural consequences of the hemodynamic disorder. It can be now supposed that hemodynamic disorders may play an additional role in the already incompetent valves and lead to further injuries to the annulus and cusps. A modern combined theory for the explanation of primary venous insufficiency can be summarized in the concept of a vicious circle *(fig. 9)* basically due to the interaction between hypotrophic structural degeneration and hemodynamic mechanical injury due to reflux.

These new aspects of venous valve pathophysiology seem to lead to a plausible explanation for the controversial results obtained by reconstructive valve surgery. Their

clinical implications are mainly represented by the need for a more careful instrumental assessment of venous valves conditions by ultrasound and/or angioscopic examination before and during reconstructive surgical procedures.

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