Medical Hypotheses 91 (2016) 73–76

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

# Dilating venous disease: Pathophysiology and a systematic aspect to different vascular territories

Ertan Yetkin [a,*], Mehmet Ileri [b]

[a] Yenisehir Hospital, Division of Cardiology, Mersin, Turkey
[b] Numune Training and Research Hospital, Department of Cardiology, Ankara, Turkey

ARTICLE INFO

*Article history:*
Received 18 November 2015
Revised 6 April 2016
Accepted 9 April 2016

*Keywords:*
Varicose vein
Varicocele
Hemorrhoid
Pelvic congestion syndrome
Varix

ABSTRACT

Venous disease is a common but overlooked clinical problem and is an important mortality and morbidity factor depending on the effected vascular territory. Different contributing factors play role on the clinical manifestation of the disease. Peripheral varices of lower extremities, hemorrhoids, varicoceles, pelvic varicose veins are the vasculopathy of veins running toward heart but against gravity. We hypothesize that all these clinical entities share common pathophysiologic steps in terms of vascular wall remodeling and vessel wall damage. A systematic approaches to both arterial and venous dilating disease in further studies and research would increase our understanding on the pathophysiology of dilating vascular disease and would provoke to find out new treatment modalities. Varicose remodeling of veins occurs by a complex interplay of various factors including both physical forces and extracellular matrix remodeling mechanisms. This article focuses on the systematic aspects of dilating venous disease with a focus on pathophysiology under the term of "Dilating Venous Disease".



## Introduction

Venous disease is a common but overlooked problem and is an important mortality and morbidity factor depending on the effected vascular territory. Both in literature and clinical practice the term chronic venous insufficiency describes a condition that affects the venous system of the lower extremities with venous hypertension and dilatation. Since varicocele or pelvic congestion syndrome is an example of chronic venous insufficiency theoretically, it is preferable to use "Dilating Venous Disease" as a general term and peripheral varicose vein or peripheral venous insufficiency, instead of chronic venous insufficiency. Vascular dilatations show a diverse clinical spectrum as in obstructive counterpart depending on the regional circulation with different clinical manifestations, and different prevalence. Coronary artery ectasia, intracranial aneurysms, aortic aneurysms and popliteal artery aneurysms are the main vascular dilatations contributing the arterial side of vascular system, throughout the body. However clinical manifestation of dilating venous disease usually occurs in the lower part of the body, in another word, lower part of the circulatory system regarding the heart in the center. Peripheral varices of lower extremities, hemorrhoids, varicoceles, pelvic varicose veins are the vasculopathy of veins running toward heart but against gravity.

## Hypothesis

Atherosclerosis has been one of the leading causes of death in the world and is a systemic disease with important squeal as a result of obstructive lesions in many regional circulations such as heart, brain, kidneys, mesentery, and limbs. In venous system, dilatation or aneurysm of the vascular wall rather than the obstructive counterpart constitutes the major health care problem. However such a systemic approach has never been paid to venous disease or dilating venous disease in different vascular territory. The main dilating venous diseases which have a major healthcare burden are peripheral varicose vein, varicocele, pelvic congestion syndrome, and hemorrhoid. Although these clinical entities have their own manifestations depending on the related organ or system, they might have arisen from the same vascular wall pathology. Regarding their vascular wall pathologies, contributing and associating factors, prevalence and their coexistence with each other, we hypothesize that they share common vascular wall pathology and needs to be evaluated under the term of dilating venous disease.

* Corresponding author.
*E-mail address:* ertanyetkin@vasmolcardiol.org (E. Yetkin).

http://dx.doi.org/10.1016/j.mehy.2016.04.016
0306-9877/

**Table 1**
Common and Divergent Features of Arterial and Venous Dilating Disease.

| | Arterial dilating disease | | | Venous dilating disease | | | |
|---|---|---|---|---|---|---|---|
| | CAE | AAA | ICA | Vcs | PCS | Hmr | PVV |
| Vascular wall degeneration and/or thinning | + | + | + | + | + | + | + |
| Prevalence (average) | 2–5% | 2–5% | 3% | 15% (M) | 10% (F) | 2–80% | 35% |
| Involvement of MMPs | + | + | + | + | | + | + |
| Involvement of cathepsin family | + | + | + | | | | + |
| Oxidative stress and/or nitric oxide | + | + | + | + | | + | + |
| Gravitational and physical forces | – | – | – | + | + | + | + |
| Coexistence with any of each other | + | + | + | + | + | + | + |
| Possible hazardous effects of nitrate | + | | | | + | | |

CAE: coronary artery ectasia, AAA: abdominal aortic aneurysm, ICA: intracranial aneurysm, VCS: varicocele, PCS: pelvic congestion syndrome, Hmr: Hemorrhoid, PVV: peripheral varicose vein, MMP: matrix metalloproteinase, M: male, F: female

## Evaluation of hypothesis

### *Varicocele*

Varicocele is a dilation of the scrotal portion of the pampiniform plexus/internal spermatic venous system that drains the testicle [1]. Varicocele is found in approximately 15% of the general population, 35% of men with primary infertility and 80% of men with secondary infertility [1]. In addition to absence or incompetence of venous valve and increased venous pressure in the pathogenesis of the disease, vascular wall pathology has also been implicated in varicocele formation [1–3]. Furthermore physical appearance and constipation has also been associated with varicocele formation [1,4,5]. Approximately 90% of varicoceles are on the left side. Differences in the anatomical configuration of the right and left internal spermatic veins may contribute to this marked left predominance [1,2]. Association of varicocele with other vascular dilating diseases has been reported in both arterial and venous regional circulation in literature. Yetkin et al. [6] has documented that patients with coronary artery ectasia, which is aneurysmal dilatation of a coronary artery, had an increased prevalence of varicocele compared with patients with coronary artery disease. Kilic et al. [7] also reported that varicocele is associated with an increased prevalence of peripheral varicose veins. Sakamoto and Ogawa [8] has demonstrated that men with bilateral varicoceles have increased mean diameter, and peak retrograde and antegrade flow velocity of the prostatic venous plexus. Therefore, varicocele, especially bilateral varicoceles, may be associated with underlying venous or vascular wall abnormalities.

Nitric oxide has been reported to be increased in the spermatic veins of men affected by varicocele [9,10]. Indeed, Shiraishi et al. [11] has demonstrated that high-grade varicocele (grades II and III) is associated with enhanced upregulation of iNOS. Alteration of extracellular matrix remodeling in terms of matrix metalloproteinases has also been postulated in the pathogenesis of varicocele in several reports [12,13]. Tissue levels of MMP-2 have been found to be higher in patients with varicocele. Moreover Serra et al. [13] has reported that MMP-9 is not only a factor for varicocele but also a common thread in inguinal hernia and chronic venous disease.

## Pelvic varicose veins

Dilatation of broad ligament and ovarian plexus veins and the presence of an incompetent ovarian vein is a specific entity known as pelvic congestion syndrome or pelvic varicocele [14]. It has been reported that pelvic varicocele occurs in 10% of the general female population and in about half of women who have chronic pelvic pain [14–16]. Both hormonal or gravitation/anatomic factors can cause venous insufficiency of the ovarian veins and/or internal iliac veins as well, leading to periovarian pelvic varicosities. Weak attachments between the adventitia of pelvic veins and surrounding connective tissue and lacking of valves are also the responsible mechanisms for pelvic varicose veins [16–19]. Histology of pelvic varicosities is similar to that of varicose veins elsewhere in the body such as peripheral varicose vein, varicocele, including fibrosis of the tunica intima and media, muscular hypertrophy and proliferation of capillary endothelium [19]. The cause of pelvic vein dilatation has not been clearly defined but estrogen induced stimulation of nitric oxide is one of the postulated mechanism in pelvic venous congestion. The majority of women affected are premenopausal, and a relationship between pelvic congestion syndrome and endogenous estrogen levels is suggested, as estrogen is known to weaken the vein walls [20]. There is a strong association between haemorrhoids and internal iliac vein reflux. Pelvic varices are frequently associated with vulvar, perineal, and lower limb varices [15,21,22]. Gultasli et al. [23] has reported high rate of venous insufficiency in lower extremities vein namely, common femoral, superficial femoral, deep femoral vein in patients with pelvic veins >5 mm in diameter.

### *Peripheral varicose vein*

The venous reflux is defined as a retrograde, downward flow in an incompetent vein connecting both poles of the ambulatory pressure gradient that occurs between the thigh and the lower leg veins during ambulation in an erect position and under the influence of gravitation [24]. Similar to the other dilating vascular diseases, histological studies have demonstrated a disruption of the organization of the extracellular matrix and smooth muscle architecture in the vessel wall of varicose veins and the marked thinning of the vessel wall at the site of the varices [25–27]. It has also been demonstrated that histological features of valvular incompetence are associated with presence of inflammatory cell infiltrates [28].

Valves in veins removed from patients with chronic venous disease show clear signs of inflammation. Monocyte/macrophage infiltration of the valve leaflets and venous wall was seen in every specimen in one surgical series, and expression of intercellular adhesion molecule-1 (ICAM-1) was elevated in the vein wall and valves in another series [29,30]. In patients with chronic peripheral varicose vein, circulating leukocytes show greater levels of activation, and their plasma shows elevated hydrogen peroxide production and also contains an activating factor for granulocytes [31]. The over expression of inducible nitric oxide synthase has been shown in varicose veins together with an increased expression of TGF-β1 and the presence of macrophages [32]. Factors regulating extracellular matrix remodeling such as MMP, TIMPs, Cathepsin enzymes, Cystatin C and plasminogen activator inhibitor have all shown to play a role in the pathogenesis [33–37]. Expression of MMP-1,-2,-9,-12, TIMP-1, and -2 has been documented to different