Pathophysiology of Varicose Veins. The Importance of Structural Proteins and Matrix Metalloproteinases

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Abstract

Varicose veins are superficial vessels that are abnormally twisted, lengthened, or dilated, and are usually caused by inefficient or defective valves within the vein. Varicose veins are part of the spectrum of chronic venous disease (CVD) which affect millions of people throughout the Western populations. A key element is the decreased amounts of collagen type III and fibronectin, resulting in inappropriate elasticity and distensibility. In addition, normal appearing saphenous vein in the same segment of varicose vein has the same structural protein deficiencies and biochemical profiles as the varicose vein. This would indicate that structural vein wall changes precede changes in valvular dysfunction. There is significant evidence in the literature that wall dysfunction consisting of alterations in the endothelium and smooth muscle cell (SMC) are a principal cause for varicose veins. Leukocytes and monocytes adhere to the endothelium as a result of elevated intercellular adhesion molecule-1 (ICAM-1), a marker of activation of leukocytes to adhere to the endothelium, which is present in CVD vein specimens but not in normal veins. These events are important steps in causing inflammation with cytokine expression and proteinase release. Matrix metalloproteinases (MMPs) are present in varicose veins, and can be found in the endothelium, smooth muscle cells, and adventitial layers of the vein wall. However it is unclear if the presence of MMPs is a result of chronic inflammation and venous wall remodeling, or are MMPs actually functional in veins causing biochemical changes in the venous wall leading to early dilation and chronic irreversible changes with extracellular matrix degradation as late stages of varicose veins. In a venous hypertension model of arteriovenous fistula it has been demonstrated that at 6 weeks there is an increased expression of MMP-2 and MMP-9 with resultant vein wall inflammation and destruction of the valve. However, using flavonoid this process is significantly abrogated implicating the importance of inflammation as an early event in venous hypertension, wall destruction and valve dysfunction, and the ability to use pharmacologic drugs to reduce the inflammatory effects. In the rat inferior vena cava, MMP-2 was demonstrated to cause venous dilation by a mechanism of hyperpolarization (a condition of negative membrane potential caused by outward potassium ion movement via specific potassium channels leading to smooth

muscle cell relaxation and resulting in venous relaxation) via large conductance calcium dependent potassium channels. In the same model it was determined that MMP-2 attenuates $[Ca^{2+}]_e$-dependent vascular smooth muscle contraction (by inhibiting Ca^{2+} entry into the smooth muscle), without affecting Ca^{2+} release from intracellular Ca^{2+} stores. In addition, to better understand the relation between tension, MMP expression, and venous dysfunction, it was demonstrated that prolonged duration with high tension (24 hours at 2 grams) caused increased expression of MMP-2 and MMP-9, with deterioration of venous contraction, compared to short duration with low tension (1 hour at 0.5 gram). There was a direct relationship between MMP expression and deterioration of venous contractility. An important question is what regulates the induction of MMPs during venous stretch and dilation. A possible mechanism may involve hypoxia inducible factors (HIF), which are nuclear transcriptional factors of heterodimeric protein consisting of α and β subunit. HIF expression may be oxygen or non-oxygen dependent including mechanical stretch. The importance of HIF is that they regulate the transcription of several target genes of oxygen homeostasis including remodeling of the extracellular matrix. In a recent study, it was determined that HIF-1α and HIF-2α were overexpressed in IVC subjected to prolonged duration with high tension. Importantly, phenylephrine-induced and KCl-induced contraction was restored in IVC exposed to prolonged duration with high tension plus the HIF inhibitor (UO126 and echinomycin). However, treatment with DMOG which stabilizes the HIF molecule, further reduced phenylephrine-induced and KCl-induced contraction in veins subjected to prolonged duration with high tension. HIF-1α and HIF-2α mRNA were overexpressed in IVC exposed to prolonged duration with high tension, and the overexpression was reversed by the inhibitors (UO126, echinomycin, and 17-DMAG) of HIF. In addition, the overexpression of HIF-1α and HIF-2α stretched IVC was associated with increased MMP-2 and MMP-9 mRNA and protein in IVC subjected to prolonged duration with high tension, but was reversed by the inhibitors (UO126, echinomycin, and 17-DMAG) of HIF, with decrease in expression of MMP-2 and MMP-9. This important study demonstrated that the regulation of MMP expression in stretched veins is tightly regulated by HIF, and offers possible pharmacologic targets to treat varicose veins.