Varicogenesis

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[FASEB J.](http://www.ncbi.nlm.nih.gov/pubmed/21685329%22%20%5Co%20%22The%20FASEB%20journal%20%3A%20official%20publication%20of%20the%20Federation%20of%20American%20Societies%20for%20Experimental%20Biology.%22%20%5Ct%20%22_blank) 2011 Oct;25(10):3613-21. Epub 2011 Jun 17.

**Experimental hypertension triggers varicosis-like maladaptive venous remodeling through activator protein-1.**

[Feldner A](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Feldner%20A%22%5BAuthor%5D" \t "_blank), [Otto H](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Otto%20H%22%5BAuthor%5D" \t "_blank), [Rewerk S](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Rewerk%20S%22%5BAuthor%5D" \t "_blank), [Hecker M](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Hecker%20M%22%5BAuthor%5D" \t "_blank), [Korff T](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Korff%20T%22%5BAuthor%5D" \t "_blank).

**Source**

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**Abstract**

An increase in circumferential wall tension (CWT) is an important determinant of vascular remodeling during hypertension or arteriosclerosis but also arteriogenesis. Although pivotal for such processes, the effect of this biomechanical force on venous remodeling has not yet been delineated. To this end, we raised the filling pressure in veins of the mouse auricle, which led to a 2.5-fold enlargement of these blood vessels within 4 d along with an increase in smooth muscle cell proliferation, matrix metalloproteinase 2 (MMP-2) expression and gelatinase activity. These changes were likewise observed in tissue samples of human varicose veins. Topical treatment of the auricles with a decoy oligonucleotide-neutralizing activator protein 1 (AP-1) inhibited these effects. Likewise, proliferation, MMP-2 expression, and gelatinase activity in both native and cultured venous smooth muscle cells exposed to enhanced stretch was decreased by up to 80% through inhibiting AP-1. In contrast, mutant control oligonucleotides had no effect on smooth muscle cell activation. These findings indicate that an increase in venous filling pressure and thus CWT is sufficient to activate AP-1, which, in turn, triggers varicose remodeling through fuelling MMP-2 activity and smooth muscle cell hyperplasia in the venous vessel wall.

[J Vasc Surg.](http://www.ncbi.nlm.nih.gov/pubmed/18502086%22%20%5Co%20%22Journal%20of%20vascular%20surgery%20%3A%20official%20publication%2C%20the%20Society%20for%20Vascular%20Surgery%20%5Band%5D%20International%20Society%20for%20Cardiovascular%20Surgery%2C%20North%20American%20Chapter.%22%20%5Ct%20%22_blank) 2008 Aug;48(2):447-56. Epub 2008 May 23.

**Prolonged increases in vein wall tension increase matrix metalloproteinases and decrease constriction in rat vena cava: Potential implications in varicose veins.**

[Raffetto JD](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Raffetto%20JD%22%5BAuthor%5D" \t "_blank), [Qiao X](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Qiao%20X%22%5BAuthor%5D" \t "_blank), [Koledova VV](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Koledova%20VV%22%5BAuthor%5D" \t "_blank), [Khalil RA](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Khalil%20RA%22%5BAuthor%5D).

**Source**

VA Boston Healthcare System, West Roxbury, Mass, USA.

**Abstract**

**BACKGROUND:**

Increased venous hydrostatic pressure plays a role in the pathogenesis of varicose veins. Increased expression of matrix metalloproteinases (MMPs) has been identified in varicose veins. Also, we have shown that MMP-2 inhibits venous contraction. However, the relation between venous pressure, MMP expression, and venous dysfunction is unclear. The purpose of this study was to test the hypothesis that prolonged increases in venous wall tension cause overexpression of MMPs and decreased contractility, which in turn promote venous dilation.

**METHODS:**

Circular segments of inferior vena cava (IVC) were isolated from male Sprague-Dawley rats and suspended between two wires in Krebs solution. Preliminary vein wall tension-contraction relation showed maximal potassium chloride (KCl) (96 mmol/L) contraction at 0.5 g basal tension, which remained steady with increases in tension up to 2 g. Vein segments were subjected to either control (0.5 g) or high (2 g) basal tension for short (1 hour) or long duration (24 hours). Isometric contraction in response to phenylephrine (Phe, 10(-5) mol/L), angiotensin II (AngII, 10(-6) mol/L), and KCl was measured. The veins were frozen to determine the expression and localization of MMPs using immunoblots and immunohistochemistry.

**RESULTS:**

In IVC segments subjected to 0.5 g tension for 1 hour, Phe and AngII produced significant contraction. At higher 2 g basal tension for 24 hours, both Phe and AngII contractions were significantly reduced. Reduction in KCl contraction was also observed at high 2 g basal tension for 24 hours, suggesting that the reduction in vein contraction is not specific to a particular receptor, and likely involves inhibition of a post-receptor contraction mechanism. In vein segments under 2 g tension for 24 hours and treated with TIMP-1, Phe, AngII, and KCl contractions were partially restored, suggesting the involvement of MMPs. IVC immunoblot analysis demonstrated prominent bands corresponding to MMP-2 and MMP-9 protein. High 2 g wall tension for 24 hours was associated with marked increase in the amount of MMP-2 and -9 relative to the housekeeping protein actin. There was a correlation between MMP expression and decreased vein contraction. Also, significant increases in MMP-2 and -9 immunostaining were observed in IVC segments subjected to high 2 g tension for 24 hours. Both MMP-2 and MMP-9 caused significant inhibition of Phe contraction in IVC segments.

**CONCLUSIONS:**

In rat IVC, increases in magnitude and duration of wall tension is associated with reduced contraction and overexpression of MMP-2 and -9. In light of our findings that MMP-2 and -9 promote IVC relaxation, the data suggest that protracted increases in venous pressure and wall tension increase MMPs expression, which in turn reduce venous contraction and lead to progressive venous dilation.

[J Vasc Surg.](http://www.ncbi.nlm.nih.gov/pubmed/17264019%22%20%5Co%20%22Journal%20of%20vascular%20surgery%20%3A%20official%20publication%2C%20the%20Society%20for%20Vascular%20Surgery%20%5Band%5D%20International%20Society%20for%20Cardiovascular%20Surgery%2C%20North%20American%20Chapter.%22%20%5Ct%20%22_blank) 2007 Feb;45(2):373-80.

**Matrix metalloproteinase 2-induced venous dilation via hyperpolarization and activation of K+ channels: relevance to varicose vein formation.**

[Raffetto JD](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Raffetto%20JD%22%5BAuthor%5D" \t "_blank), [Ross RL](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Ross%20RL%22%5BAuthor%5D" \t "_blank), [Khalil RA](http://www.ncbi.nlm.nih.gov/pubmed?term=%22Khalil%20RA%22%5BAuthor%5D" \t "_blank).

**Source**

VA Boston Healthcare System, West Roxbury, MA, USA.

**Abstract**

**BACKGROUND:**

Varicose veins are a common disorder of extensive venous dilation and remodeling with an as-yet unclear mechanism. Studies have shown increased plasma and tissue levels of matrix metalloproteinases (MMPs) in human varicose veins and animal models of venous hypertension. Although the effects of MMPs are generally attributed to extracellular matrix degradation, their effects on the mechanisms of venous contraction/relaxation are unclear. Our preliminary experiments have demonstrated that MMP-2 causes inhibition of phenylephrine-induced venous contraction. The purpose of this study was to determine whether MMP-induced inhibition of venous contraction involves an endothelium-dependent and/or -independent pathway.

**METHODS:**

Circular segments of the inferior vena cava (IVC) were isolated from male Sprague-Dawley rats and suspended between two wire hooks in a tissue bath, and the effects of MMP-2 on phenylephrine- and KCl-induced contraction were measured. To study the role of endothelium-derived vasodilators, experiments were performed in the presence and absence of endothelium; N(G)-l-nitro-arginine methyl ester (L-NAME), an inhibitor of nitric oxide synthesis; indomethacin, an inhibitor of prostacyclin synthesis; cromakalim, an activator of adenosine triphosphate-sensitive K+ channels (K(ATP)); and iberiotoxin, a blocker of large-conductance Ca2+-dependent K+ channels (BK(Ca)) and smooth muscle hyperpolarization.

**RESULTS:**

In endothelium-intact IVC segments, phenylephrine (10(-5) mol/L) caused significant contraction that slowly declined to 82.0% in 30 minutes. The addition of MMP-2 (1 microg/mL) caused a gradual decrease of phenylephrine contraction to 39.5% at 30 minutes. In endothelium-denuded IVC, MMP-2 induced a greater reduction of phenylephrine contraction, to 7.6%. In the presence of L-NAME (10(-4) mol/L), MMP-2 caused a marked decrease in phenylephrine contraction, to 4.4%. Large MMP-2-induced inhibition of phenylephrine contraction was also observed in IVC treated with L-NAME plus indomethacin. MMP-2 caused relaxation of phenylephrine contraction in IVC pretreated with cromakalim (10(-7) mol/L), an activator of K(ATP) channels. MMP-2-induced inhibition of phenylephrine contraction was abrogated in the presence of iberiotoxin (10(-8) mol/L), a blocker of BK(Ca). MMP-2 did not inhibit venous contraction during membrane depolarization by 96 mmol/L KCl, a condition that prevents outward K+ conductance and cell hyperpolarization.

**CONCLUSIONS:**

MMP-2 causes significant IVC relaxation that is potentiated in the absence of endothelium or during blockade of endothelium-mediated nitric oxide and prostacyclin synthesis. The lack of effects of MMP-2 on KCl contraction and in iberiotoxin-treated veins suggests MMP-2-induced smooth muscle hyperpolarization and activation of BK(Ca) channels--a novel effect of MMP that may play a role in the early stages of venous dilation and varicose vein formation.