

Abstracts

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Inhibitory Effects of Calcitonin Gene-Related Peptides on Experimental Vein Graft Disease

Zhang X, Zhuang J, Wu H, et al. *Ann Thorac Surg* 2010;90:117-23.

Conclusion: Transfection of calcitonin gene-related peptide inhibits inflammatory mediator expression, macrophage infiltration, and neointimal hyperplasia in experimental vein graft disease.

Summary: The mechanisms of intimal hyperplasia are complex, and include interactions with inflammatory cells, inflammatory mediators, and smooth muscle cells. In particular, macrophages appear necessary for the initiation of intimal hyperplasia. Calcitonin gene-related peptide (CGRP) is a biologically active amino peptide, 37 amino acids in length. Studies have shown that CGRP can inhibit inflammatory cells and expression of inflammatory mediators such as tumor necrosis factor (TNF)- α and MCP-1 that appear important in intimal hyperplasia (Li W, et al, *Am J Cell Physiol* 2006;291:C456-65). CGRP can also inhibit hyperplasia of vascular smooth muscle and protect endothelial cell function (Deng W, et al, *Life Sci* 2006;78:1830-8 and Ye F, et al, *Vasc Pharm* 2007;46:238-46). The authors sought to evaluate the effects of CGRP expressed by an adeno-associated virus vector (AAV2) gene transfer on macrophage infiltration and inflammatory mediators of vein graft disease in a rabbit model. The hypothesis was that the transfected CGRP gene could inhibit macrophage infiltration and expression of inflammatory mediators and thus suppress intimal hyperplasia.

Rabbit jugular vein grafts were incubated *ex vivo* in a solution of adeno-associated virus vectors containing the CGRP gene (AAV2/*L.CGRP*) or *Escherichia coli* B-galactosidase (*LacZ*), or a saline solution. These grafts were then interposed in the carotid artery. CGRP gene expression was identified by a reverse transcription polymerase chain reaction (PCR) and *LacZ* gene expression was identified by X-gal staining. At 4 weeks, intima/media ratios were determined, and macrophages were identified with CD68 antibody immunohistochemistry. Inflammatory mediators were measured with real-time PCR. *CGRP* and *LacZ* gene expression were positive at 4 weeks postoperatively. The intima/media ratio was significantly inhibited in the AAV2/*L.CGRP* group. Also significantly inhibited in the AAV2/*L.CGRP* group were monocyte chemoattractant protein-1, TNF- α , inducible nitric oxide synthase, and matrix metalloproteinase-9. Macrophage infiltration was also inhibited.

Comment: The authors' experiment supported their hypothesis. The report is brief and does not delineate specific patterns of gene expression and thus does not allow precise determination of mechanism. However, the end result—very effective inhibition of intimal hyperplasia—is interesting. Vascular and cardiovascular surgeons remember the recent disappointments of the PREVENT 3 and PREVENT 4 trials, where novel therapy directed at the genetic level failed to suppress intimal hyperplasia. With respect to inhibiting intimal hyperplasia, the chiasm between promising basic bench research and clinical relevance in humans remains wide. This is interesting work, but given the history of this field, any optimism should be tempered with caution.

Leiomyosarcoma of the Inferior Vena Cava: Clinicopathologic Study of 40 Cases

Laskin WB, Fanburg-Smith JC, Burke AP, et al. *Am J Surg Pathol* 2010;34:1873-81.

Conclusion: Macroscopic resection of a localized vena cava leiomyosarcoma is the best chance for long-term survival. Suprahepatic tumors are associated with early death, and compromised liver function correlates with overall poor survival.

Summary: Leiomyosarcoma is the most common sarcoma that affects the venous system, and nearly 50% arise in the inferior vena cava (Kavorkian J, Cento DP, *Surgery* 1973;73:390-400). However, leiomyosarcoma of the inferior vena cava accounts for only about 0.5% of adult soft tissue sarcomas (Hollebeck ST, et al, *J Am Coll Surg* 2003;197:575-9). Overall prognosis is thought to be poor, with metastatic disease occurring primarily to liver and lung, and recurrent disease contributing to tumor-related mortality as well.

In this report, the authors detailed the clinical pathologic features and follow-up data on 40 patients with inferior vena cava leiomyosarcoma. The study cohort consisted of 31 women and 9 men (mean age, 53 years) whose material was accessioned to the Armed Forces Institute of Pathology between 1976 and 2008. Median tumor size was 8.5 cm (range, 2.5-15.0 cm). The middle segment of the inferior vena cava was most often involved. Most tumors grew extraluminally. Eleven of the 33 patients managed by complete radical resection had involved surgical margins. Twenty of 34 patients with clinical follow-up died of sarcoma-related complications, and 26% died of unknown causes. Survival rates after resection without documented residual

macroscopic disease were 50% at 5 years and 22% at 10 years. Factors that statistically correlated with death at ≤ 2 years were suprahepatic vena cava involvement, right atrial involvement, predominantly intraluminal tumor growth, and residual postsurgical macroscopic disease. Univariate analysis suggested intraluminal tumor ($P = .03$), liver entry or failure ($P = .01$), and moderate to poor tumor differentiation ($P = .03$) were associated with increased tumor-related mortality. On multivariate analysis, only compromised liver function ($P = .01$) correlated with mortality.

Comment: This is a very large series of leiomyosarcoma of the inferior vena cava and confirms a poor prognosis associated with these tumors and the seemingly obvious fact that incomplete resection is associated with a poor short-term survival. Nevertheless, it is interesting to note that the growth pattern extraluminal vs intraluminal and the status of the patient's overall hepatic function also appear to be important prognostic factors in patients with this rare malignancy.

Randomized Clinical Trial of VNUS® ClosureFAST™ Radiofrequency Ablation versus Laser for Varicose Veins

Shepherd AC, Gohel MS, Brown LC, et al. *Br J Surg* 2010;97:810-8.

Conclusion: Radiofrequency ablation (RFA) using VNUS ClosureFAST (VNUS Medical Technologies, San Jose, Calif) is associated with less postprocedural pain than endovenous laser ablation (EVLA). Clinical and quality of life improvements for the two procedures are similar at 6 weeks.

Summary: Endovenous ablative procedures have largely replaced standard saphenous stripping for treatment of saphenous reflux in patients with primary varicose veins. At the time of publication of this article, only one small randomized trial has compared VNUS ClosureFAST and EVLA (Almeida JJ et al, *J Vasc Interv Radiol* 2009;20:752-9). This current study compares the most utilized technique for EVLA in Great Britain (980-nm wavelength and bare fiber) vs the most popular RFA system in Great Britain (VNUS ClosureFAST). Consecutive patients with primary great saphenous vein reflux were randomized to EVLA or RFA at a single center. The primary outcome measure was postprocedural pain at 3 days. Secondary outcome measures were quality of life at 6 weeks, as determined by the Aberdeen Varicose Vein Questionnaire (AVVQ) and Short Form 12 (SF-12), and clinical improvement using the Venous Clinical Severity Score (VCSS). Analysis was on an intention-to-treat basis. There were 64 patients randomized to EVLA and 67 to RFA. At 3 days, mean (SD) pain scores were 26.4 (22.1) mm for RFA and 36.8 (22.5) mm for EVLA ($P = .010$). Over 10 days, mean (SD) pain scores were 22.0 (19.8) mm for RFA vs 34.3 (21.1) mm for EVLA respectively ($P = .001$). Mean number of analgesic tablets used over 3 days and over 10 days was lower for RFA ($P = .003$) than EVLA ($P = .001$). There were no differences in AVVQ, SF-12, and VCSS scores at 6 weeks between the two groups ($P = .887$, $P = .076$, $P = .449$, respectively).

Comment: The study demonstrated that VNUS ClosureFAST results in significantly less pain than 980-nm EVLA for ablation of the great saphenous veins in treatment of patients with varicose veins. The study supports previous publications that demonstrate less postprocedural pain after RFA but failed to show differences in outcomes after 1 month (Morrison N, *Semin Vasc Surg* 2005;18:15-8 and Almeida J, et al, *J Vasc Interv Radiol* 2009;20:752-9). However, EVLA is continuing to be refined. There are newer fibers with longer wave lengths and jacketed laser fibers that appear to be associated with lower postintervention pain scores (Almeida J, et al, *Vasc Endovasc Surg* 2009;43:467-72). Data comparing these new devices with VNUS closure system will also eventually be required.

Recurrent Deep Vein Thrombosis: Long-Term Incidence and Natural History

Labropoulos N, Jen J, Jen H, et al. *Ann Surg* 2010;251:749-53.

Conclusion: Deep vein thrombosis (DVT) recurrence is associated with age > 65 and an elevated residual thrombus burden. Pulmonary embolism (PE) occurs frequently and is a common cause of death.

Summary: The reported incidence of recurrent venous thromboembolism (VTE) is up to 40% at 10 years (Prandoni P, *Hematologica* 2007; 92:199-205), with most recurrent VTE occurring after anticoagulation has been discontinued. Whereas much is known about recurrent DVT, there are actually few long-term studies examining factors influencing recurrent DVT and its natural history. The authors enrolled both inpatients and outpatients with acute DVT in their study. They excluded patients with previous VTE, active cancer, those already on anticoagulation, or those requiring permanent anticoagulation. Also excluded were patients with short life expectancy