

Cardiac Effects In The Multiple Sclerosis Patient – Implications For Avoidance Of Restenosis After CCSVI Angioplasty

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Introduction

Multiple sclerosis patients suffer from numerous neurological and inflammatory symptoms and signs. For this reason, focus on this disease process and appropriate treatments has been centered on the neurological insults to the brain and central nervous system, and more recently, has included evidence of abnormal venous drainage from the brain (CCSVI – “Chronic Cerebrospinal Venous Insufficiency”) and related abnormal fluid dynamics. Little attention has been paid to the cardiac effects of multiple sclerosis, but a review of literature indicates that such evaluation may provide critical information as to the pathogenesis and treatment of multiple sclerosis, including reducing the frequency of restenosis in the patient treated with angioplasty for CCSVI.

A review of the literature indicates that multiple sclerosis patients (as studied by Akgul F, et al) demonstrate subclinical left ventricular diastolic dysfunction ($P < 0.05$). The cause of left ventricular diastolic dysfunction (when not secondary to medications such as mitoxantrone) is the overproduction of inflammatory cytokines such as TNF-alpha (Tumor Necrosis-alpha), Interleukin-6 (IL-6) and Interleukin-1 (IL-1) – all are mast cell mediators.

For approximately a decade, these inflammatory cytokines have been implicated in the development and progression of heart failure. Additionally, TNF-alpha is known to promote and activate thromboembolism. The actions of such inflammatory cytokines in combination with the activation of Matrix Metalloproteinase (MMP) is assumed to cause collagen breakdown in the heart, and cardiac mast cells play an important role in the initiation of this process.

Similar changes of collagen are occurring in the veins of patients with CCSVI. The study of mast cells and their granulations is critical when reviewing the potential causes of CCSVI and the avoidance of restenosis in the CCSVI patient.

Purpose

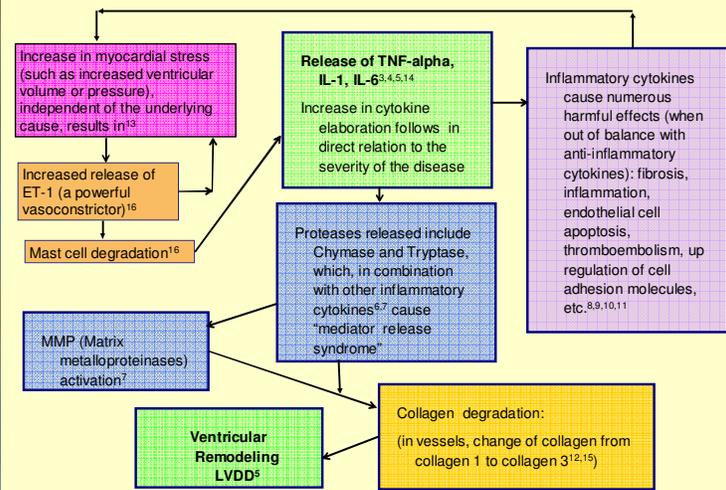
M.S. patients develop left ventricular diastolic dysfunction (LVDD).¹

Ehlers-Danlos Syndrome (EDS) patients also develop LVDD.² Many, if not all, EDS patients who develop autonomic dysfunction also have CCSVI.

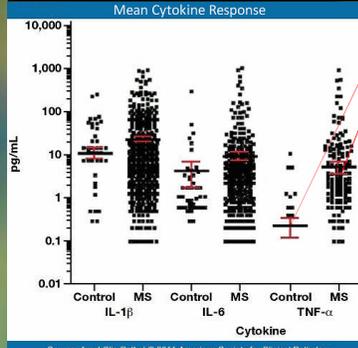
What occurs on a molecular and chemical level in LVDD and congestive heart failure? Can the cause of the changes seen in myocardial tissue reflect the disease process in M.S. and/or the cause of restenosis?

Can this information give us new targets for treatment of M.S. and PREVENTION OF RESTENOSIS?

Methods/Result: Literature Review



Inflammatory cytokines are higher in the MS patient



Red whiskers indicate the standard error of the mean cytokine response in MS patients vs. normals.

Reference:
* Diagram: Martins T, Rose J, et al. Analysis of Proinflammatory and Anti-inflammatory Cytokine Serum Concentrations in Patients with Multiple Sclerosis by Using a Multiplexed Immuno assay. Amer J of Clin Path. 2011;136(5):696-704

Conclusion:

Understanding the mechanisms involved in LVDD in the M.S. or EDS patient, and accepting that vascular changes are part of the disease process in both conditions, new and unique opportunities for treatment and prevention of restenosis come to light.

New medications may include those that block histamine (H1 and H2 antagonists), mast cell stabilizers (cromolyn sodium and ketotifen), leukotriene blockers (montelukast), prostaglandin blockers (aspirin), flavinoids (including quercetin and luteolin), juaubi.

TNF-alpha blockers: many medications for rheumatoid arthritis target TNF-alpha, but new medications with fewer side effects are also available.

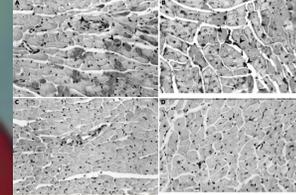
IL-1 blockers (anakinra, and many IL-6 blockers), Chymase inhibitors

ET-1 blockers: bosentan, sitaxentan, ambisentan

IL-6 blockers (statins, aspirin, indomethacin)

Mast cell trigger avoidance should be considered as part of the post-angioplasty protocol.

Inflammatory Cytokines + MMP = collagen change



Collagen 1 becomes Collagen 3

Potential Effects of TNF-alpha in Heart Failure: Could these effects also contribute to restenosis?

- Produces left ventricular dysfunction
- Produces pulmonary edema in humans
- Produces cardiomyopathy in humans
- Activates thromboembolism experimentally
- Promotes thromboembolism experimentally
- Promotes abnormalities in myocardial metabolism experimentally
- Produces B-receptor uncoupling from adenylate cyclase experimentally
- Abnormalities in mitochondrial energetics
- Activation of the fetal gene program experimentally
- Produces cardiac myocyte apoptosis experimentally



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