The Cardiovascular Cure

Endothelial Health

About This Article

This article, originally written by Joan Beal for MS patients and caregivers on ThisIsMS.com, began as an early exploration of the connection between MS and the endothelium. Written before Dr. Zamboni's work had been made available, information for this paper was sourced from many scientific articles on the endothelium available online, as well as from Dr. John Cooke's book on endothelial health for the vascular system, *The Cardiovascular Cure*.

That the endothelium plays a critical role in development of MS lesions has now been clearly established.[1,2,3,4] While the effects of CCSVI on endothelial function remain theoretical, many researchers believe that there may be a link between the abnormal venous blood flow caused by CCSVI and endothelial stress and dysfunction[5].

Beyond MS, endothelial health (or dysfunction) has been associated with a wide range of diseases, including heart disease, diabetes, arthritis, renal dysfunction, Lupus, Parkinson's and many others.

The aim of this presentation is to "connect the dots" across a wide range of studies and ideas, summarizing current research about endothelial health and preservation. While we hope to inform our readers about the many ways that environmental and nutritional factors contribute to endothelial health, we must also stress that this information is purely educational; ***all medical or nutritional decisions should be made in consultation with medical professionals***.

Endothelial Health and Maintenance

By **Joan Beal**
With Al Ossorio

Understanding the Endothelium

There are approximately 60,000 miles of blood vessels in an adult human body. This vast network of arteries, veins and capillaries is maintained and a protected by an inner sheath of microscopic cells called “endothelial” cells (from the Greek “endo” meaning within, and “thiele” meaning nipple, which together suggest “deep within our breast”). These many hundreds of thousands of cells, together comprising the “endothelium,” form the inner lining of blood vessels and lymph vessels, forming a thin layer between the vessel walls and the flowing blood, and serving as an interface between the blood and the rest or our body.

Once considered merely an inert “Teflon-like” inner lining of the blood vessels, the endothelium is now understood to be the single largest secreting organ in the body. Further, the endothelium is highly active in regulating circulatory stability through blood pressure functions (e.g. vessel dilation and contraction), inflammatory processes, and coagulation.

The Role of Nitric Oxide in the Vascular System

In the early 1980s, after having established that the endothelium played a surprisingly active role our vascular system, researchers Robert F. Furchgott and Louis J. Ignarro sought what was called the EDRF, or the “endothelium-derived relaxing factor,” an unknown signaling mechanism through which the endothelium could communicate with and regulate surrounding vascular tissues. During their research, Furchgott and Ignarro independently discovered that the healthy endothelium secretes substances which protect vascular health. Chief among these is nitric-oxide, a tiny two-atom gas, which is now considered the hallmark of normal endothelial function and the elusive “signaling factor” they had been searching for. Importantly, this was the first time that a gas had been implicated as a signaling mechanism in any biological system, let alone in the human body. For this remarkable discovery, Furchgott and Ignarro, together with Dr. Ferid Murad (who had initially proposed that a gas could be controlling aspects of vascular function) were awarded the Nobel Prize in medicine in 1998.

Building on Furchgott et al.’s work, it has now been established that Nitric Oxide (NO) is involved in local regulation of critical processes, including:

- Vascular tone
- Inflammation
- Coagulation
- Oxidation

If these processes are not strictly regulated, they can lead to impaired vascular health, potentially creating atherosclerosis, cardiovascular, and autoimmune disease[6] .Further, NO has been show to protect the heart, stimulate the brain, and kill bacteria, thus playing a pivotal role in a wide variety of diseases and conditions[7].

If the endothelium becomes damaged and the NO levels become imbalanced, cells which should remain in the blood can leak through blood vessels and into adjacent body tissue. Some of the leaked cells can include proteins, such as the C-Reactive protein, which is produced by the liver and causes inflammation[8]. By inhibiting NO, endothelial signaling can become impaired, and disease may result. Because the endothelium actively maintains approximately 60,000 miles of blood vessels in our body, endothelial dysfunction has been linked to a wide variety of diseases, including:*

- Diabetes
- Atherosclerosis
- Heart disease and Stroke
- Hypertension
- Multiple sclerosis
- Lupus
- Scleroderma
- Rheumatoid arthritis
- ALS
- Parkinson's
- Hypercoagulation of blood, thrombosis, clotting disorders
- Renal Failure
- Metabolic Syndrome- abdominal obesity, hypertension, insulin resistance
- Sleep Apnea (as a cause of endothelial dysfunction)
- Glaucoma

Given that a wide body of research has established the role of the endothelium (and nitric oxide) in the overall health of the human body, the importance of understanding how the endothelium becomes damaged, and how to prevent that damage, becomes clear.

Aside from genetic mutations, which may contribute to endothelial dysfunction, various studies and clinical trials have helped establish at least some of the causes of endothelial damage, as well as suggest some preventative measures. It should be noted, however, that any given person's risk of endothelial dysfunction is difficult to define, and the exact point at which exposure to damaging agents moves from *potential* damage to *actual* damage is difficult to quantify. Additionally, to counteract toxin exposure, our bodies contain efficient systems for removing waste. For example, our liver, kidneys and lymphatic system all work to remove toxins from our bodies. Unfortunately, despite our bodies' defenses, our lifestyles may be exposing us to more toxicity than our natural cleaning and maintenance systems can handle. However, our increasing understanding of the endothelium has allowed us to identify potential sources of damage, and to suggest likely preventative measures.

Potential Causes of endothelial dysfunction

1. Oxidative stress

Our bodies constantly react with oxygen as we breathe and as our cells produce energy. However, our use of oxygen is a double-edged sword: we need oxygen to survive, but as a consequence of using oxygen, highly reactive molecules, known as "free radicals," are produced. Free radicals are atoms or molecules with electrons which have lost their partner electron, often as a result of our respiratory or metabolic process, or from outside influences. Free radicals can disrupt the balance of NO, damage the endothelium and leave it overly permeable, allowing toxins to pass into our tissues[9]. In most instances, our body has an adequate supply of antioxidants obtained from food to neutralize these free radicals, but if the body is depleted, or if there are too many coexistent factors, injury to the endothelium and a change in the balance of NO may occur.

Factors which can increase the number of free radicals in our bodies include:

- Plastics, especially PCBs and BPA[10]
- Smoking and second hand smoke. Smoking reduces nitric oxide in the blood vessels and causes an increase in ADMA, the modified amino acid which puts strain on the heart. Nicotine also causes vessels to narrow, so that less oxygen is delivered to the heart. Platelets become stickier, and therefore clot formation is increased. Additionally, smoking raises the level of carbon monoxide in the blood, which increases the risk of injury to endothelial cells[11]
- Metals exposure, including mercury and cadmium[12]
- Air pollution, especially diesel exhaust[13]
- Arsenic and chlorine[14] (which can sometimes be found in drinking water)

2. Eating Bad fats

   Some fats are not good for our bodies and should be avoided. Heavily saturated animal and dairy fats, trans fats, hydrogenated fats and chemically-

3. altered fats from vegetable shortening and oils can all damage the endothelium[15].

4. Stress

   Cortisol, the hormone released into the body when we are under acute stress, impairs endothelial production[16]

5. Sleep deprivation

   Lack of restful sleep, due to obstructive sleep apnea (or, potentially, oxygen deprived sleep), or not enough time in bed, may create endothelial dysfunction and constricted blood flow[17].

6. Acute Bacterial infections
   Chlamydia pneumonia, Lyme disease, Sepsis, Staph - all of these infections can become chronic as the endothelium is weakened, and bacteria may enter body tissues, compromising or impairing the immune system[18].
7. Low Vitamin D levels
   A lack of sunshine and dietary vitamin D has been shown to be harmful to the endothelium[19].
8. Low Vitamin B12 levels
   Low vitamin B12 creates high levels of homocysteine in the blood (a sulfur containing amino acid) which damages the endothelium. An unbalanced diet, a strict vegetarian diet that excludes all meat, fish, dairy and eggs diet, or a diet overly reliant on processed foods, could all lead to low vitamin B12 levels, potentially damaging the endothelium[20].
9. High glucose intake
   Ingesting too much glucose in the form of simple sugars increases endothelial cell death and increases oxidative stress[21].
10. Sedentary Lifestyle
    Lack of physical exertion, especially cardio-vascular exercise, damages the endothelium[22].

Preserving and enhancing Endothelial health

Research suggests several methods for restoring the endothelium to its healthy natural state, potentially relieving inflammation, normalizing blood pressure, and minimizing the harmful effects of C-Reactive protein or various antigens that may cross the blood brain barrier. Healthy endothelium is largely impermeable to unnecessary breaches of the blood brain barrier, thus protecting central nervous system tissue.

Endothelial health is not achieved through a single pill or a simple cure. The process of endothelial restoration is multifaceted, and takes discipline and dedication. Again, please note that this information is purely informational – *all dietary or nutritional decisions should be made in conjunction with your physician or medical professional.*

1. Physical Activity
   Physical activity has been shown to stop endothelial dysfunction, especially cardiovascular exercise. Inactivity increases the breakdown of the blood vessels. A sedentary lifestyle is not beneficial to the endothelium; daily moderate exercise is recommended[23].
2. Stress reduction
   Reducing stress through lifestyle changes can reduce endothelial damaging cortisol. While no single stress reduction technique works for everyone, common options include meditation, visualization, exercise, mindful communication, prayer (for those of faith), and intentional breathing practices such as tai chi and yoga.
3. Promote healthy liver function
   Milk Thistle, an herb derived from a flowering thistle plant (sometimes sold as "Legalon"), contains an active liver-protecting agent called silymarin. This substance, which actually consists of a group of compounds called flavonolignans, helps repair liver cells damaged by toxic substances. Silymarin also helps prevent new liver cells from
4. being destroyed by toxins, reduces inflammation, and has potent antioxidant effects. Sylmarin has been shown to protect the endothelium[24]. Note: alcohol and other substances known to damage the liver should be consumed only in moderation (or avoided altogether).
5. Promote vitamin D intake
   Given that vitamin D is derived from sunlight, spend time outdoors. Skin makes vitamin D when exposed to ultraviolet B (UVB) radiation from the sun. Because of sunscreen and our indoor lives, many people are not receiving enough of this potent vitamin. Vitamin D acts as a hormone in our bodies, working with the parathyroid to keep proper levels of calcium in our blood. It can also be taken as a supplement. Research on the efficacy of various types of vitamin D supplements is still on-going; we encourage anyone interested in vitamin D supplements to investigate current recommendations with their physician.
6. Laugh!
   A University of Maryland study showed that healthy men and women who were shown a

funny movie increased blood flow by 22% and improved vascular and endothelial health. The effects of laughter lasted for 45 minutes after the movie had finished.

7. Nutrition and supplements (eat healthy food; avoid processed foods)

   Avoid processed foods whenever possible. Not only do processed foods often contain high levels of salt, which is linked to vascular problems, preservatives and various chemicals for coloring and flavoring, but recent research has shown a strong correlation between production and consumption of processed foods and MS[25].

   Eating a diet of whole foods (unprocessed foods; foods that retain the natural state) provide ample levels of nutrition and antioxidants, supplements can also be taken to help our body reach optimal nutritional levels. Antioxidants bind with free radicals to minimize the damage they cause to the endothelium. Vitamin A and carotenoids are found in carrots, squash, broccoli, sweet potatoes, tomatoes, kale, collards, cantaloupe, peaches and apricots (brightly-colored fruits and vegetables) Vitamin B is common in fish, meat and dairy products. Vitamin B12 is frequently used in combination with other B vitamins in a vitamin B complex formulation. This helps maintain healthy nerve cells and red blood cells and is also needed to make DNA, the genetic material in all cells. Vitamin C is found in citrus fruits like oranges and limes, green peppers, broccoli, green
8. leafy vegetables, strawberries and tomatoes. Vitamin E is plentiful in nuts & seeds, whole grains, green leafy vegetables, olive oil. Flavonoids, a specific kind of antioxidants from plant pigments, reduce inflammation and improve vascular health. Quercetin, found in apple skin, red onion, red grapes, as well as ECGC (found in green tea), also contain important antioxidants and nutrients.
9. Healthy fats

   Salmon, trout, herring, avocados, olives, walnuts, and olive oil all contain
10. healthy fats. An omega-3 fish oil supplement is important, particularly if you do not have fish in your diet. Current research suggests that the most important fish oil fatty acid is docosahexaenoic acid (DHA). We have long known that fish is healthy, but it is now proven that the omega-3s in fish fat improve endothelial function by enhancing nitrec oxide production, increasing HDL (good) cholesterol levels, and reducing LDL (bad)
11. cholesterol and triglyceride levels. Further, fish oils have been shown to reduce production of free radicals and substances that cause inflammation in the body[26].
12. Healthy Proteins

    Reducing red meat proteins in your diet and replacing them with vegetable and soy proteins will help the endothelium. Animal proteins contain mixtures of amino acids that produce more of the amino acid methionine, which is the precursor for homocysteine,

which can damage the endothelium. Vegetable proteins are healthier because they contain no saturated fat and less methionine. Vegetable proteins also have more fiber and nutrients called phytonutrients. Soy proteins produce a mixture of amino acids that have more L-arginine. L-arginine is essential for the production of NO. Soy proteins also contain other phytochemicals - the biochemical products of plants - which are healthy for the endothelium. Other L-arginine sources include fish, nuts, legumes, beans and chicken[27].

13. Probiotics

    Probiotics are live microorganisms (in most cases, bacteria) that are similar to beneficial microorganisms found in the human gut. They are also called "friendly bacteria" or "good bacteria." Probiotics are available to consumers mainly in the form of dietary supplements and foods like yogurt.

14. Essential Minerals

    Studies have shown that magnesium, zinc, and calcium are all important to preserving endothelial health[28,29]. Look for supplements which contain all three of these minerals in balance

15. Antithrombic and Anti-inflammatory Herbs

    Curcumin, Salvia, Ginko, and Garlic are all shown to decrease inflammation and regulate blood viscosity, preventing hypercoagulation. Proteolytic Enzymes, both serrapeptase and nattokinase, are enzymes which reduce inflammation and pain and help blood viscosity by regulating clotting. Bromelain, found in pineapple, is one of the best anti-inflammatory substances known.

* = References for the association between endothelial health and these syndromes and diseases are widely available on-line

References:

1. Adams, et al. Periventricular Lesions on Mlutiple Sclerosis: Their Perivenous Origin and Relationship to Granular Ependymitis.(1987) *Neuropathology and Applied Neurobiology*. Vol 13:41-152
2. Kermode, et al. (1990) Breakdown of the Blood-Brain Barrier Precedes Symptoms and Other MRI Signs of New Lesions in Multiple Sclerosis. *Brain*. 113: 1477-1489
3. Ge et al. (2008) 7T MRI: New Vision of Microvascular Abnormalities in Multiple Sclerosis. *Archives of Neurology*. 65(6): 812-816
4. McQuaid, et al. (2009) The effects of blood-brain barrier disruption on glial cell function in multiple sclerosis. *2nd Neuroscience Ireland Conference*. 37: 329-3

5. Simka, M. (2008) Blood Brain Barrier Compromise with Endothelial Inflammation may Lead to Autoimmune Loss of Myelin during Multiple Sclerosis. Current Neurovascular Research, 6 (2); 1-8
6. Kolb, H. and Kolb-Bachofen, V. 1998. Nitric oxide in autoimmune disease: cytotoxic or regulatory mediator? *Immunology Today*,19 (12), 556-561
7. The Nobel Assembly at Karolinska Institute, (1998). *Press Release; The Nobel Prize in Physiology or Medicine, 1998*. Retrieved March 12, 2010, from http://nobelprize.org/nobel_prizes/medicine/laureates/1998/press.html
8. 20. *Sridevi Devaraj, Uma Singh and Ishwarlal Jialal (2009). The Evolving Role of C-Reactive Protein in Atherothrombosis. Clinical Chemistry, 55, 229-238*
9. *21*. Rubanyi, GM, Vanhoutte, PM., (1986). Superoxide anions and hyperoxia inactivate endothelium-derived relaxing factor(s). *American Journal of Physiology.* **250:**H822-H827.
10. Hennig B., Hammock B.D., Slim R., Toborek M., Saraswathi V., Robertson L.W. (2002) PCB-induced oxidative stress in endothelial cells: modulation by nutrients. *International Journal of Hygiene and Environmental Health*, volume 205, March 2002 pp. 95-102
11. Kalliopi Karatzi, MSc, Christos Papamichael, MD, Emmanouil Karatzis, MD, Theodore G. Papaioannou, PhD, Paraskevi Th. Voidonikola, MD, John Lekakis, MD and Antonis Zampelas, PhD. Acute smoking induces endothelium dysfunction (2007*). Journal of the American College of Nutrition*, Vol. 26, No. 1, 10–15
12. *Houston, M.C. (2007).* The role of mercury and cadmium heavy metals in vascular disease, hypertension, coronary heart disease, and myocardial infarction. *Alternative Therapies in Health and Medicine*, 13(2):S128-33
13. Håkan Törnqvis, Nicholas L. Mills, Manuel Gonzalez, Mark R. Miller, Simon D. Robinson, Ian L. Megson, William MacNee, Ken Donaldson, Stefan Söderberg, David E. Newby, Thomas Sandström, and Anders Blomberg (2007). *American Journal of Respiratory and Critical Care Medicine,* Vol 176. pp. 395-400
14. Yu Chen, Regina M. Santella, Muhammad G. Kibriya, Qiao Wang, Maya Kappil, Wendy J. Verret, Joseph H. Graziano, Ahsan Habibul (2007) Association between arsenic exposure from drinking water and plasma levels of soluble cell adhesion molecules. *Environmental Health Perspectives* 115:1415-1420
15. 14 Robert T. Gerber, Kathleen Holemans, Ivan O'Brien-Coker, Anthony I. Mallet, Rita Bree,F. André Assche, Lucilla Poston (1999). Cholesterol-independent endothelial dysfunction in virgin and pregnant rats fed a diet high in saturated fat. *The Journal of Physiology*, Volume 517 (2), pp. 607-616
16. *Andrew J.M. Broadley, Ania Korszun, Eltigani Abdelaal, Valentina Moskvina, John Deanfield, Christopher J.H. Jones and Michael P. Frenneaux (2006).* Metyrapone Improves Endothelial Dysfunction in Patients With Treated Depression. *Journal of the American College of Cardiology*, 48:170-175
17. 22. El Solh Ali A.; AKINNUSI Morohunfolu E.; BADDOURA Fadi H., MANKOWSKI Corey R. (2007). Endothelial cell apoptosis in obstructive sleep apnea : A link to endothelial dysfunction. *American journal of respiratory and critical care medicine*, 175 (11), 1186-1191.
18. Adler, Robert, *Psychoneuroimmunology*. pp 958-960
19. Ozlem Tarcin, Dilek Yavuz, Ahmet Toprak, Ahu Telli, Meral Yuksel, Dilek Yazici, Seda Sancak, Oguzhan Deyneli, Goncagul Haklar, Sema Akalin (2007). Effect of vitamin D replacement on endothelial function and oxidative stress in vitamin D deficient subjects. *Endocrine Abstracts* Vol. 14, 275
20. American Heart Association (2010, May). Homocysteine, Folic Acid and Cardiovascular Disease. Retrieved 29 June, 2010, from

http://www.heart.org/HEARTORG/GettingHealthy/NutritionCenter/Homocysteine-Folic-Acid-and-Cardiovascular-Disease_UCM_305997_Article.jsp

21. . Ludovica Piconi 1, Lisa Quagliaro, Roberta Assaloni, Roberto Da Ros, Amabile Maier, Gianni Zuodar, Antonio Ceriello (2006). Constant and intermittent high glucose enhances endothelial cell apoptosis
22. through mitochondrial superoxide overproduction. *Diabetes and Metabolism Research and Review*. May-Jun;22(3):198-203.
23. lrich Laufs; Sven Wassmann; Thomas Czech; Thomas Münzel; Marco Eisenhauer; Michael Böhm; Georg Nickenig (2005). Physical Inactivity Increases Oxidative Stress, Endothelial Dysfunction, and Atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 25:809.
24. Higashi Y, Sasaki S, Kurisu S. (1999). Regular aerobic exercise augments endothelium-dependent vascular relaxation in normotensive as well as hypertensive subjects: role of endothelium-derived nitric oxide. *Circulation.* 1999;100:1194–1202
25. Szilard S, Szentgyorgyi G, Dhanalakshmi S et al. (1988). Protective effect of Legalon in workers exposed to organic solvents. *Acta Med Hung*. **45**:249-256.
26. Medical News Today. (2010, June). ENS 2010: German Comparative Clinical Trial: Margarine, Processed Meats And Other Foods Can Increase The Risk Of Multiple Sclerosis. Retrieved 29 June, 2010, from http://www.medicalnewstoday.com/articles/193051.php
27. Lakatta, Ed G. (2009). How to Promote and Maintain a Healthy Endothelium, Article XV. Retrieved 10 March, 2010 from http://healthandage.org/professional/how-to-promote-and-maintain-a-healthy-endothelium-article-xv-part-3-of-4
28. Maria Annunziata Carluccio; Luisa Siculella; Maria Assunta Ancora; Marika Massaro; Egeria Scoditti; Carlo Storelli; Francesco Visioli; Alessandro Distante; Raffaele De Caterina (2003). Olive Oil and Red Wine Antioxidant Polyphenols Inhibit Endothelial Activation. *Arteriosclerosis, Thrombosis, and Vascular Biology.* 2003;23:622.
29. Meerarani, P Ramadass, Michal Toborek, Hans-Christian Bauer, Hannelore Bauer and Bernhard Hennig (2000). Zinc protects against apoptosis of endothelial cells induced by linoleic acid and tumor necrosis factor 1,2,3. *American Journal of Clinical Nutrition*, Vol. 71, No. 1, 81-87
30. Yiqing Song, Tricia Y Li, Rob M van Dam, JoAnn E Manson and Frank B Hu (2007). Magnesium intake and plasma concentrations of markers of systemic inflammation and endothelial dysfunction in women. *The American Journal of Clinical Nutrition*. Apr;85(4):1068-74