Cardiac Fibrotic Remodeling – The Role of Fibrosis in LAF

INTRODUCTION

Atrial fibrosis – is it simply the result of AF which then causes more episodes or might it be that fibrotic remodeling as a result of aging leads to AF?

Or is the natural decline of fibrolytic enzymes at fault? Further, might we consider the oxidative stress connection? And let's also examine the evidence suggesting the pro-fibrotic effects of magnesium deficiency.

These questions were posed to me by Erling Waller ex-afibber (75) who thinks there may be a connection. His afib began at 64 and then 10 years later, after some nutritional adjustments, his AF vanished. (See his story in Hans' book.)

Erling has been a regular and prolific contributor of important information and was always generous with his time and support to help others seeking answers. He continues to ponder the origin of AF and finds the fibrosis remodeling connection not only intriguing but also plausible. Erling is tackling another remodeling project at the moment and asked me to present this topic to the BB.

Interrelated factors in the "Fibrotic Remodeling Theory"

I. Fibrosis mechanism
II. Mechanisms of AF
III. Inflammation and C-reactive Protein
IV. Oxidative Stress and Nitric Oxide/Peroxynitrite production
V. Magnesium deficiency

BACKGROUND

First, you must go to this site and view the color photo of a fibrotic heart and the quick time video of electrically-stimulated cardiac myocyte contracting. Keep the image of this heart in your memory as you consider fibrosis as a connection to AF.

http://www.clevelandclinic.org/heartcenter/pub/atrial_fibrillation/AFresearch.htm

This paper published by the CCF, states that atrial fibrosis is simply the result of atrial fibrillation (AF). Author and researcher David Van Wagoner, PhD, bases his conclusion on research studies. (1)

Let's begin –

I. Fibrosis: the body's natural scar formation or healing defense-mechanism. When functioning optimally, and in response to injury, too much reparative fibrin is always laid down and then lysed (broken down) by fibrolytic enzymes; then removed from the body via the circulatory system.

Research shows that around age 27, the body begins to build fibrotic tissue because of a decline in fibrolytic enzymes production. In atrial fibrillation, this could explain why younger people are frequently affected and also why the general age group for the onset of AF seems to be around the age of 60 years. Some individuals lack fibrolytic enzyme production ability at earlier ages than others. (Biochemical individuality.)

A logical discussion on the role of fibrosis – in terms of our causative investigation – comes from William Wong PhD, a Classical Naturopath, Exercise Physiologist, Certified Athletic Trainer (AATA), Certified Sports Medicine Trainer (ASMA) in his article, " **Fibrosis - Enemy of Life."** (2) He says:

> "In all of us as we age (after 27), fibrosis grows inside of all of our internal organs diminishing their size and with that shrinkage comes a diminution of function. Med school anatomy teaches this lowering of function is what ultimately leads to us dying as the organs fail due to weakness.
>
> … this leads to the question: Why does this seem to start after 27? At or around 27 our own production of proteolytic enzymes drops.

We make a finite amount of enzymes in a lifetime and use about half of that by 25. (That's the reason why young folks, though they make cancer cells from the first day of life don't usually develop that or most any of the other conditions mentioned, they have an adequate supply of proteolytic enzymes to fight off fibrosis

It is after our supply of proteolytic enzymes drops to be spread through the rest of our lifetime that we begin to develop the fibrosis conditions.

(For you docs out there it's my contention that we can measure a pre morbid state from taking measures of proteolytic enzymes just as we can predict death within 3 days by measuring the levels of Dopamine. Useful diagnostic tool maybe. Nifty research tool certainly).

So if we can deal with the laying down of fibrosis as efficiently as we did as youngsters, then we would avoid or reduce much of what is trying to shorten our lives or at least make us sick or less able.

The most important thing to put back into an aging body is are not vitamins and minerals, not herbs, not the growth hormones but enzymes, the proteolytic enzymes.

Vitamins and minerals are more properly named co enzymes and co factors in other words they are things that help enzymes to work. If the enzymes aren't there to begin with, then the vitamins and minerals have little to work on and little action.

That's the reason why vitamin / mineral supplementation works so well for some and does not do squat for others, they have little of the enzymes they need to work on.

If we put in some of the primary protein-eating enzymes, then the body will cause the *"enzyme cascade"* creating thousands of new enzymes from the original 4 or 5.

Regarding fibrin…. all proteolytic enzymes eat away at fibrin (fibrinolysis) to some degree but some are considerably stronger at that than others. If the proteolytic enzymes you put back are also very highly fibrinolytic then the scar tissue your body has been creating WILL be taken away.

(This is a secret that plastic surgeons, internists and pulmonologists i.e. lung doctors, are learning about systemic enzymes). The fibrin that is supposed to be there is marked by the body as an endogenous protein, in other words something that is supposed to be part of your structure, but excesses in fibrin, though deposited by the body, are marked as exogenous proteins - or as something not belonging in the body.

Remember excesses in fibrin equal:

* weak structure, (by not leaving enough space for epithelial tissue to grow through the fibrin matrix),

* restriction of range of motion (joints and muscles)

* diminution of size and function (internal organs).

(End of Wong quote.)

Conclusions in "Cardioreparation in Hypertensive Heart Disease" (HHD) (3)

This paper addresses cardiac fibrotic remodeling in general; not resulting from AF but rather, from hypertensive heart disease(HHD). Note the author is addressing structural remodeling and treatment by cardioprotective or cardioreparative strategies which support Wong's findings.

Quote:
The potential to regress cardiac fibrosis by ACE inhibition and to reverse ventricular diastolic dysfunction is supported by experimental studies in rats with genetic hypertension and the recent clinical trial by Brilla et all in patients with HHD.

The importance of pathologic structural remodeling, not simply the control of arterial pressure, needs to be addressed in recognizing that quality, not quantity, of myocardium in HHD is responsible for adverse cardiovascular events, management must no longer solely focus on a regression in left ventricular mass. Far more desirable is a regression of left ventricular mass and fibrosis with correction of ventricular dysfunction.

Moreover, cardioprotective and cardioreparative interventions specifically target such remodeling with the view toward respectively preventing or regressing cardiac fibrosis in HHD and in so doing favorably influencing adverse risk."

This article suggests the adverse accumulation of matrix protein be reduced by proteolytic digestion…a cardioreparative measure. (3) End quote (Be sure to read this article.)

II. MECHANISMS: ATRIAL FIBRILLATION

AF is a progressive disease; numerous lines of evidence suggest that disease progression results from cumulative electrophysiological and structural remodeling of the atria.(5) Ongoing events coupled with fibrotic remodeling perpetuate longer episodes. (4)

In many patients, AF begins with short episodes, typically characterized as "palpitations" (a fluttering sensation in the chest), or "paroxysms."
Over time, there is a tendency for these episodes to become longer. Why does this happen? Once AF has been initiated, the atria undergo a process known as "remodeling." (1)

Structural changes: (remodeling) In time, afib that persists for years, is also accompanied by significant degenerative structural changes. (1)

- Individual muscle cells within the fibrillating atria tend to become elongated and sometimes wider. AF-induced atrial remodeling causes both structural and electrical changes(1)
- Fibrosis: In addition, the space between individual myocytes typically becomes more fibrotic, with fatty infiltration, and the atria is less able to contract. (1)

Electrical changes: (remodeling)

- Fibrillating atria tend to have more complicated patterns of electrical activity. This is due both to the increased fibrosis, and to intrinsic changes in the electrical activity in the atrial myocytes. Research at the CCF has helped to characterize the electrical remodeling process associated with long-standing AF. (1)

- The net result is that in patients with persistent AF, the atria are more able to sustain fibrillatory activity, due to the combined effects of both structural and electrical remodeling. (1)

Atrial Electrical Remodeling (sustains afib) Refer to the video web page.

- The net result of the electrical and structural changes is that the enlarged atria are more likely to sustain fibrillatory activity. Thus, AF can persist for a longer duration in the remodeled atria. (1)

- Calcium ions have an important role in both the electrical and contractile activity of the heart. Thus, calcium overload is implicated as an early event in the electrical remodeling process. (1)

- Persistent AF results in further changes in protein expression, loss of myofibrillar structure, and eventually myocyte death and replacement fibrosis. (1)

Atrial Structural Remodeling

The fibrillating atria are subjected to continuous, high rate electrical activity (with rates up to 500 per minute). This results in impaired atrial contractility, and the initiation of structural changes. (Be sure to look at the picture of a heart exhibiting AF-induced fibrosis and the stained fibrotic-tissue studies.) (1)

- At the macroscopic level, structural remodeling is frequently characterized by increased atrial fibrosis and fatty infiltration, both on the endocardial surface, and between muscle bundles. (1)
- At the microscopic level, fibrosis can isolate muscle bundles. (1)
- *(Key Point)* It is evident that fibrosis can isolate muscle bundles and that this can alter the pathway of electrical activation, creating a substrate that can promote the persistence of atrial fibrillation. (1)

IONIC REMODELING IN THE HEART

Pathophysiological Significance and New Therapeutic Opportunities for Atrial Fibrillation (*Circulation Research.* 2000;87:440.) © 2000 American Heart Association, Inc.

Heart disease has long been recognized to alter cardiac electrical function. Detailed studies of disease-induced remodeling of ionic transport processes that underlie ventricular electrophysiological alterations have been performed over the past 10 years, but our knowledge of atrial ionic remodeling is more limited and has emerged much more recently.

(This) review focuses on recent findings regarding ionic remodeling at the atrial level, particularly with respect to two conditions that promote atrial fibrillation (AF) in well-developed clinically relevant animal models: (1) sustained atrial tachycardia and (2) ventricular tachypacing–induced congestive heart failure.

Morphology of atrial myocardium in human pulmonary veins: a postmortem analysis in patients with and without atrial fibrillation. (Pub Med)

….. significant differences in the histology of PVs between the two groups were a higher frequency of discontinuity and hypertrophy and a higher degree of fibrosis of the atrial myocardium in the PVs of patients with AF.

Atrial myocardium was more often present in the PVs of patients with compared with patients without AF. In the first group, the atrial myocardium in the PVs was characterized by more severe discontinuity, hypertrophy, and fibrosis. A marked variation in anatomical dimensions of the PVs existed.

Atrial fibrillation: the tip of the iceberg. Arch Mal Coeur Vaiss. 2002 Sep; 95(9): 827-32.

Atrial fibrillation (AF) usually results from profound alterations of the functional properties and structure of the atrial myocardium.

The electrical remodeling of diseased atria is most often associated with severe tissular and cellular alterations including: fibrosis, myocyte dystrophy with myolysis and dedifferentiation, apoptosis and gap junction disorganization. These abnormalities could result from a common and non specific adaptive response to changes in the working conditions of the atrial myocardium

Electrical remodeling in atrial fibrillation. Time course and mechanisms. Circulation. 1996 Dec 1; 94(11): 2968-74.

Atrial fibrillation is self-perpetuating, suggesting that the tachyarrhythmia causes electrophysiological changes that contribute to the progressive nature of the disease. In animal models, pacing-induced rapid atrial rates result in sustained atrial fibrillation. This is mediated by shortening of refractory periods termed electrical remodeling. The purpose of the present study was to characterize the time course of electrical remodeling and to define mechanisms of the phenomenon.

Atrial electrical remodeling develops quickly, is progressive, and may be persistent. Shifts in autonomic tone, atrial stretch, or depletion of high-energy phosphates do not contribute significantly to the phenomenon. Results of the study suggest that atrial electrical remodeling is mediated by rate-induced intracellular calcium overload.

III Inflammation and C-Reactive Protein

What about the role of inflammation and afib as indicated by elevated C-reactive protein markers? Now proven to be elevated in people with varying degrees of AF, CRP is not only a marker or risk factor indicating heart disease, but is also common in afib.(6) Which came first? The inflammation or the AF?

C-reactive protein elevation in patients with atrial arrhythmias: inflammatory mechanisms and persistence of atrial fibrillation. Circulation. 2001 Dec 11; 104(24): 2886-91.

Conclusions: CRP is elevated in AF patients. This study is the first to document elevated CRP in non-postoperative arrhythmia patients. These findings are reinforced by stepwise CRP elevation with higher AF burden. Although the cause of elevated CRP levels in AF patients remains unknown, elevated CRP may reflect an inflammatory state that promotes the persistence of AF. (6)

Ascorbate attenuates atrial pacing-induced peroxynitrite formation and electrical remodeling and decreases the incidence of postoperative atrial fibrillation. Circ Res. 2001 Sep 14; 89(6): E32-8.

(Ascorbate equates to Vitamin C – a strong anti-oxidant and anti-inflammatory agent)

We have recently demonstrated that chronic human AF is associated with increased atrial oxidative stress and peroxynitrite formation.

In chronically instrumented dogs, we found that rapid (400 min(-1)) atrial pacing was associated with attenuation of the atrial effective refractory period (ERP). Treatment with ascorbate, an antioxidant and peroxynitrite decomposition catalyst, did not directly modify the ERP, but attenuated the pacing-induced atrial ERP shortening following 24 to 48 hours of pacing.

Biochemical studies revealed that pacing was associated with decreased tissue ascorbate levels and increased protein nitration (a biomarker of peroxynitrite formation). Oral ascorbate supplementation attenuated both of these changes

Patients receiving ascorbate had a 16.3% incidence of postoperative AF, compared with 34.9% in control subjects.

IV. Oxidative Stress and Nitric Oxide/Peroxynitrite production

In an overview article written by David R. Van Wagoner, PhD, of the CCF, entitled “Molecular Basis of Atrial Fibrillation: A Dream or A Reality,” (4) he indicates his published study (5) on this topic focused on the pathways related to oxidant injury and inflammation signaling.

It was found that increased protein tyrosine nitration was evident in atrial tissues from patients in permanent AF, which is highly suggestive of increased peroxynitrite formation (due to avid interaction of nitric oxide and superoxide anion). He observes that oxidative stress may underlie structural and contractile changes in the fibrillating atria. Also observed in animal pacing studies (also published)(6), pretreatment and daily supplementation of dogs with high dose ascorbate (as an antioxidant) was associated with a significant decrease in protein nitration.

He speculates that the left atrium may be preferentially sensitive to oxidative stresses, due to either lower metabolic reserves or increased wall stresses.

What is the Connection Between Oxidative Stress and AF?
(Here is peroxynitrite again. Be sure to review this section in the CCF(1) article.)

- AF is associated with calcium overload. This can increase the production of nitric oxide (NO), and mitochondrial free radical production.
- AF is associated with neurohormonal activation, frequently leading to increased production of Angiotensin II (and superoxide).
- Our research (in collaboration with colleagues at the Ohio State University) has shown that, as a result of increased NO and/or superoxide production, protein nitration is increased during persistent AF, suggesting increased peroxynitrite formation.
- This relationship suggests that, in some circumstances, antioxidants may help to prevent the cellular injury and electrical changes that normally accompany AF. Several studies have been completed to evaluate this hypothesis, and others are ongoing.

Impaired Myofibrillar Energetics and Oxidative Injury During Human Atrial Fibrillation
http://circ.ahajournals.org/cgi/content/abstract/104/2/174

Atrial fibrillation (AF) is associated with severe contractile dysfunction and structural and electrophysiological remodeling.

Mechanisms responsible for impaired contractility are undefined, and current therapies do not address this dysfunction. We have found that myofibrillar creatine kinase (MM-CK), an important controller of myocyte contractility, is highly sensitive to oxidative injury, and we hypothesized that increased oxidative stress and energetic impairment during AF could contribute to contractile dysfunction.

The present results provide novel evidence of oxidative damage in human AF that altered myofibrillar energetics may contribute to atrial contractile dysfunction and that protein nitration may be an important participant in this condition.

IV. MAGNESIUM DEFICIENCY

This survey would not be complete without examining the role of magnesium deficiency (MgD).

Pattern of cardiac fibrosis in rabbits periodically fed a magnesium-restricted diet and administered rare earth chloride through drinking water.
It has been postulated that causation of the tropical cardiomyopathy endomyocardial fibrosis (EMF) is linked to magnesium (Mg) deficiency and cardiac toxicity of the rare earth (chloride) element cerium (Ce).

The results suggest that in rabbits, recurrent episodes of Mg deficiency lead to myocardial fibrosis similar to the pattern observed in human EMF.
(This article can be found by title at PubMed Online)

Magnesium deficiency-related changes in lipid peroxidation and collagen metabolism in vivo in rat heart.
Int J Biochem Cell Biol. 1997 Jan;29(1):129-34.

Magnesium deficiency is known to produce a cardiomyopathy, characterized by myocardial necrosis and fibrosis.

(This) study provides evidence of increased lipid peroxidation and net deposition of collagen in the myocardium in response to dietary deficiency of magnesium.

It is suggested that the increase in cardiac collagen synthesis and fibroplasia associated with Mg deficiency may represent reparative fibrogenesis, upon oxidative damage to the cardiac muscle, and is mediated by a mechanism independent of changes in cardiac tissue levels of Mg.

Pro-fibrogenic effects of magnesium deficiency in the cardiovascular system. Magnes Res. 2002 Dec;15(3-4):307-15.

Magnesium deficiency is known to produce cardiovascular injury. A large body of experimental evidence supports the postulation that an immuno-inflammatory reaction and increased oxidative stress may damage the myocardium and vasculature in magnesium deficiency. Reparative/reactive fibrosis in response to the injury has, however, received little attention.

Recent evidence from a rodent model of acute magnesium deficiency suggests that humoral factors may activate cardiac fibroblasts by a free radical-mediated mechanism and contribute to cardiac fibrogenesis. A similar mechanism may also promote cellular hyperplasia and increased matrix synthesis in the vasculature.

Magnesium Deficiency in the Pathogenesis of Mitral Valve Prolapse (8)
This paper specifically related to Mitral Valve Prolapse (MVP) and MgD, includes important statements:

- MVP contributes to cardiac arrhythmia. Mg therapy provides relief of MVP symptoms.
- MgD hinders the mechanism by which fibroblasts degrade defective collagen, increases circulating catecholamines, predisposes to cardiac arrhythmias, thromboembolic phenomena and dysregulation of the immune and autonomic nervous systems.
- *Durlach* et al. considered all their patients to be Mg-deficient, based on blood Mg levels. They also suggest that complications of MVP such as cardiac arrhythmia, thromboembolism and neurasthenia may all have the same cause: Mg-D.
- Some important aspects of the MVP syndrome cannot be explained by chronic Mg-D alone: its pathology, which suggests a dyscollagenosis, the association with autoimmune thyroid disorders and the complexity of dysautonomia.
- Mg-deficient animals show enhanced adrenergic responsiveness due to lack of induced down-regulation of P-receptors MVP patients, on the other hand, are extremely sensitive to P-blockade, and may show excessive a-adrenergic and parasympathetic tone. Experimental Mg-D produces myocardial collagen deposition whereas MVP is associated with valvular collagen dissolution. These paradoxes might be explained by a failure of cAMP-dependent mechanisms.
- Fibroblasts continually produce defective collagen and delete it by a process which is cAMP activated]. Adenylate cyclase is Mg dependent and Mg-D is associated with defective activity of some cAMP-dependent pathways. If MVP were indeed a genetic disorder of connective tissue, its penetrance would be enhanced by any condition which impairs the ability of fibroblasts to delete defective collagen.
- Another means by which chronic Mg-D might affect cAMP activity is impairment of essential fatty acid (EFA) metabolism. Patients with normocalcernic LT show elevation of linoleic acid in plasma phospholipids and decreased levels of its desaturation products.
- PGEI is an important determinant of cellular cAMP activity. It stimulates fibroblast collagen degradation and enhances the maturation of cytotoxic/suppressor lymphocytes PGEI protects against autoimmune phenomena; its deficiency may predispose to autoimmunity and also to fibrosis.

Conclusion

Most features of the MVP syndrome can be attributed to direct physiological effects of MgD or to secondary effects produced by blockade of EFA desaturation. These include valvular collagen dissolution, ventricular hyperkinesis, cardiac arrhythmias, occasional thromboembolic phenomena. autonomic dysregulation and association with LT, pelvic fibrosis, autoimmune disease, anxiety disorders, allergy and chronic candidiasis. (8)

From the Lancet, "**Extraordinary unremitting endurance exercise and permanent** injury to normal heart"(9) author William J. Rowe, MD, observes:

"…..magnesium ion deficiency, which can be induced by exercise, could exacerbate two vicious cycles: severe ischaemia and high catecholamines, the second would be between coronary vasospasm (induced by high catecholamines) and endothelial injury and also contribute to catecholamine-induced thrombogenesis.

In addition to ischaemia, there are several mechanisms, including the effect of free fatty acids liberated by the lipolytic effect of high catecholamines, that could cause direct myocardial injury.

Magnesium ion deficiency is a further possible complication of long exercise, some deficiency may still be present 3 months later. Exposure to heat also contributes to magnesium ion deficiency. The increase in catecholamine concentration may persist until the second day after a marathon. It is noteworthy that in a group of 20 patients with vasospastic (variant) angina showed that almost half had magnesium ion deficiency that is often unrecognised.

Accompanying this paper is a flow chart describing biochemical reactions in very long endurance exercise. It is worth noting where High Shear Stress Turbulence fits in with Endothelial injury. See this chart on the last page before references. (9)

A collaboration of researchers in a paper on the **Role of Magnesium in Aging**, (10) concludes:

- Aging leads to a higher requirement for magnesium.
- Cells lose magnesium mono exponentially with age.
- One of the biological changes associated with aging is an increase in free radical formation with subsequent damage to cellular processes.
- The consequences of stress susceptibility, defective membrane functions and perturbation of intracellular calcium metabolism, inflammation, cardiovascular diseases including atherosclerosis and ischaemia/reoxygenation injury, diabetes, fibrosis, immune dysfunction and other diseases associated with aging

Superoxide-mediated activation of cardiac fibroblasts by serum factors in hypomagnesemia. Free Radic Biol Med. 2001 Oct 1;31(7):882-6.

Magnesium deficiency is known to produce myocardial fibrosis in different animal models.

The findings are consistent with the postulation that serum factors may activate cardiac fibroblasts via a superoxide-mediated mechanism and contribute to the fibrogenic response in the heart in magnesium deficiency.

Model of cardiovascular injury in magnesium deficiency. Med Hypotheses. 2001 Jan;56(1):110-3.

Magnesium deficiency is known to produce cardiovascular lesions. It is, however, not clear as to what constitutes magnesium deficiency - reduced serum levels, reduced tissue levels or reduced intracellular levels of the ionic form of the element. This article cites evidence in support of a hypothesis that a fall in serum magnesium levels may trigger a temporal sequence of events involving vasoconstriction, hemodynamic alterations and vascular endothelial injury to produce pro-inflammatory, pro-oxidant and pro-fibrogenic effects, resulting in initial perivascular myocardial fibrosis which, in turn, would cause myocardial damage and replacement fibrosis. Further, angiotensin II may be the prime mover of the pathogenetic cascade in magnesium deficiency. Importantly, such a mechanism of cardiovascular injury would be independent of a reduction in myocardial or vascular tissue levels of magnesium.

CONCLUSIONS

If you have followed along this fibrosis path and examined the relationships of possible contributing factors, the question remains…..What are the connections? What ties it all together?

Taking PC's summary of the Pall papers presented in the CR on the NMDA receptor, the production of nitric oxide and the resultant cytotoxic product, peroxinitrate, might we hypothesize that this production (from whatever stimulus) leads to irritation and fibrosis?

Dr. Wong tells us that Fibromyalgia and CFS share a common etiology in excess nitric oxide and peroxynitrite. He says FM pain originates because … "Growing too much fibrin (scar tissue) on contractile (muscle) tissue binds down that tissue causing a localized ischemia.(7)

He relates that years back, …. "while Max Wolf, MD, Ph.D. (x7) was teaching at Fordam and researching at Columbia, he came to an interesting discovery most of us are only partially familiar with. This author of the first medical textbook on endocrinology found that old age begins at 27. This is triggered by a down turn in the body's

production of proteolytic enzymes. Aside from their familiar but secondary role in digestion, proteolytic enzymes have four primary functions in mammals:

- First line of defense against inflammation. Enzymes cleave Circulating Immune Complexes it sees as being excessive in number or exogenous to the body.
- Balances the bodies repair mechanism preventing excessive fibrin from being deposited in wounds, fractures and across joints or moving parts.
- Cleans the blood of necrotic debris and excesses of fibrin.
- Modulates immune function as an adaptogen." (7)

Can we state there is a connection between lack of fibrolytic enzymes and the creating of fibrosis in the body – specifically in the heart and this is the cause of AF? Certainly studies are indicating that fibrosis prolongs or perpetuates it.

Is the Oxidative Stress factor significant enough of an irritant to suggest that fibrosis is the result of the body's natural defense mechanism to an injury or insult…. the laying down of fibrin…. and if one is lacking sufficient production of the proteolytic enzymes that break down excess fibrin, then does the person end up with cardiac fibrosis?

Obviously, we would like to connect the dots to these plausible, causative factors associated with atrial fibrillation.

However, this survey is just that… a collection of relevant studies and papers …just a few out of a huge amount of resources.

What do you think? Is Erling on to something here?

I'm sure he'll be reading your opinions with interest. For now, I'm going with the lack of fibrolytic enzymes theory. I may change my mind after I read your comments.

Sorry this is so lengthy, but I tried to spare you going back and forth to the Internet with reference articles to allow the flow of this hypothesis….. you will need to read many of the featured studies in detail, however, to get the total concept.

I'm looking forward to your response.

Jackie

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