THE AFIB REPORT

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The Inflammation Connection

Inflammation is the body's immediate response to an injury, infection or other type of stress. It is usually time limited and ceases when healing is completed. However, in some cases the inflammatory response continues unchecked and this can lead to the development of inflammatory diseases such as asthma, rheumatoid arthritis, and Crohn's disease. An elevated erythrocyte (red blood cell) sedimentation rate (ESR) and high blood levels of interleukin-6 (IL-6) and C-reactive protein (CRP) are prominent features of inflammation.

There is mounting evidence that a systemic inflammation of the blood vessel lining is heavily involved in the initiation and progression of atherosclerosis. Austrian researchers have found that chronic dental infections, urinary tract infections, and chronic respiratory infections all substantially increase the risk of atherosclerosis[1]. Italian researchers have found elevated blood levels of IL-6 and CRP in patients with unstable angina and have associated such higher levels with an increased risk of heart attacks[2]. Very recently researchers at the Harvard Medical School found that high CRP levels are a potent risk factor for peripheral arterial disease (intermittent claudication)[3].

Just recently diabetes, depression, and most common cancers were also added to the list of inflammatory diseases[4,5,6]. It is probably not an overstatement to conclude that over 90% of all that ails us is caused by an underlying inflammation.

So why are we so inflamed? There are several possible explanations:

- Our lifestyle often emphasizes factors that are known to initiate inflammation – mental, emotional and physical stress, vigorous exercise, alcohol consumption, mercury poisoning (mostly from dental amalgams), and oxidative stress. Inflammation can also be initiated by a bacterial, viral or fungal infection.

- Many common foods are inflammatory given the right conditions. The excessively high ratio of omega-6 polyunsaturated fatty acids to omega-3 fatty acids found in our modern diet favours the production of inflammatory prostaglandins, which certainly does not help matters[7].

- Childhood exposure to bacteria and viruses has been sharply curtailed through vaccinations and an excessive preoccupation with cleanliness. According to the "hygiene hypothesis" this has created an imbalance in the body's T-cells (key immune system defenders) so that the ones that promote inflammation have become dominant[8].

Whatever the reason, there is no doubt that inflammation and the many diseases resulting from it are rampant today.

Inflammation and LAF

Could an inflammation be involved in lone atrial fibrillation (LAF)? Indeed it could. In 1997 Dr. Andrea Frustaci, MD and colleagues at the Catholic University of Rome made a fascinating discovery. They performed biopsies of the right atrium in 12 patients with LAF and found that 8 (67%) of them had evidence of a current or past inflammation in the heart tissue (myocarditis). They also checked 11 control subjects and found that none of their biopsy samples showed any signs of inflammation. The Italian researchers conclude that inflammation and its aftermath (fibrotic tissue) is a likely cause of LAF[9].

The inflammation was found to be active in 3 of the 8 patients. These patients were treated with the anti-inflammatory medication prednisone. They had no further LAF episodes over a 2-year follow-up. The remaining patients were treated with propafenone, sotalol, flecainide or amiodarone and had numerous LAF episodes over the next 2 years.

Through recent correspondence with Dr. Frustaci I learned that 2 more patients had later shown signs of active inflammation and had been successfully treated with prednisone[10]. Dr. Frustaci concurred that a relapse of atrial inflammation could result in new episodes of LAF and that it is quite possible that all of the 12 LAF patients actually had signs of inflammation, but that the biopsy missed them in four of the cases. Dr. Frustaci also agreed that a high concentration of mercury or antimony in the heart tissue could produce electrical instability perhaps leading to LAF. Dr. Frustaci has earlier reported that some patients with congestive heart failure have levels of mercury and antimony in their heart tissue that are 22,000 and 12,000 times higher respectively than those found in healthy people[11]. Canadian researchers at the University of Calgary have pointed out that dental amalgams (silver fillings) would be the most likely source of the mercury[12].

More recently Dr. Frustaci and colleagues reported a link between ventricular arrhythmias (tachyarrhythmias) and the presence of inflammation in the left ventricle. The inflammation in turn was linked to the presence of hepatitis C virus, enterovirus or influenza virus in the inflamed tissue[13].

American and Greek researchers have found that many patients with congestive heart failure also have an active inflammation of the heart lining which, in some cases, can be treated successfully with prednisone. They observed that about one third of the patients with active inflammation had elevated erythrocyte sedimentation rates[14,15]. It is intriguing to speculate about a possible link between Dr. Frustaci's findings of grossly elevated levels of mercury and antimony in the heart tissue of patients with congestive heart failure and this new finding.

In January 2002 two research papers were published that clearly support the inflammation connection[16,17]. Both papers, one by American researchers (Cleveland Clinic) and one by Greek researchers, report a significant association between the level of C-reactive protein (CRP), a marker of inflammation, and the presence and severity of LAF.

The Cleveland Clinic researchers tested CRP levels in patients with atrial fibrillation (AF) and compared them to the levels in control patients with no history of AF. Sixty-seven of the AF patients had lone atrial fibrillation which was defined as AF in the absence of structural heart disease; patients with hypertension and LAF, but no structural heart disease were also included in this group. The LAF group was further divided into those with paroxysmal LAF (defined in this study as episodes self-terminating within 30 days) and those with persistent LAF (episodes lasting longer than 30 days, but amenable to cardioversion).

The researchers found that patients with AF, with or without structural heart disease, had significantly higher blood levels of CRP than did controls (median value of 0.21 mg/dL versus

0.096 mg/dL). The average value for LAF patients was 0.21 mg/dL, which was not significantly lower than that found in AF patients with structural heart disease (0.23 mg/dL). CRP levels were generally higher if the patients were actually in atrial fibrillation or had come out of an episode within 24 hours of sampling. These patients had average CRP values of 0.30 mg/dL as compared to 0.15 mg/dL for AF patients in sinus rhythm. It was also clear that patients with persistent AF had higher CRP values than patients with paroxysmal AF (0.34 mg/dL versus 0.18 mg/dL).

The researchers conclude that AF might induce or be induced by an inflammation, which in turn may promote the persistence of AF. They suggest that CRP levels may become useful in predicting stroke risk and need for warfarin therapy in AF patients. They also suggest that clinical trials of the use of anti-inflammatory agents in the prevention of AF may be warranted.

The Greek researchers tested CRP levels in 50 paroxysmal AF patients who were actually in fibrillation at the time of sampling and compared results to those obtained for 50 people in normal sinus rhythm. The AF patients had a median CRP level of 0.80 mg/dL as compared to 0.04 mg/dL for controls. The researchers observed that AF patients who could not be cardioverted had a much higher average CRP level (2.12 mg/dL) than did patients who were successfully cardioverted (0.50 mg/dL). They also noted that patients with an enlarged left atrium had considerably less success in being cardioverted. They conclude that high CRP levels are strongly associated with the presence of AF and with a lower chance of successful cardioversion.

Source of LAF

It is profoundly interesting and revealing that most of the triggers for LAF identified in our survey are associated with an inflammatory response. Mental and physical stress, vigorous exercise, alcohol consumption, mercury poisoning, bacterial, viral and fungal infections and oxidative stress have all been identified as potential initiators of inflammation[1,18-22]. There is also a distinct association between autonomic nervous system dysfunction and the inflammatory response[23,24]. Animal experiments have shown that an excessive release of norepinephrine (noradrenaline) can cause an inflammation and conversely that an inflammation can damage the nerve endings that release norepinephrine[25,26].

The connection between the autonomic nervous system and inflammation is indeed an intriguing one and may well hold the key to the origin of LAF. Please note that the following is pure speculation on my part and not supported by any clinical evidence that I am aware of.

It would seem that LAF requires the presence of both an inflammation of the heart lining (myocarditis) and an imbalance in the autonomic nervous system. Is it possible that this combination of inflammation and autonomic nervous system dysfunction could trigger the damage to nerve endings (vagal or adrenergic) in the myocardium? Is it also possible that the body would compensate for this damage by increasing the output of norepinephrine (the adrenergic transmitter) and acetylcholine (the parasympathetic [vagal] transmitter) at adjacent nerve endings? If this were indeed the case it would explain the creation of highly sensitive *foci* on the surface of the heart. These *foci* in turn would initiate an LAF episode whenever the dominant (unbalanced) branch (adrenergic or vagal) of the autonomic nervous system became overloaded through physical or mental stress, etc. The highly sensitive *foci* would be discernible during an electrophysiology study and would be the ones destroyed during ablation therapy. Again I want to emphasize that this hypothesis is pure speculation on my part; however, it does seem to make sense and could be a plausible explanation for the initiation and continuation of LAF episodes.

Elimination of LAF

Dr. Frustaci believes that individual heart cells, which have been exposed to inflammation, can revert to normal cell structure – assuming that the DNA of the cell has not been damaged beyond repair. This is indeed encouraging as it may mean that LAF could be permanently eliminated if the inflammation is vanquished [10].

So how can the inflammation be eliminated? Clearly a two-pronged approach is required:

- The causes (triggers), which bring on flare-ups of inflammation, must be avoided.
- The immune system must be rebalanced to prevent an excessive inflammatory response.

Cutting out alcohol, caffeine, cold drinks, MSG, aspartame etc. is the easy part. The most difficult part for many afibbers, especially those with the vagal variety, will be to refrain from vigorous exercise and work-outs until the inflammation has subsided. This is absolutely essential though. Exercise will fan the inflammation; as a matter of fact Harrison's "Principles of Internal Medicine" suggests that bed rest may be necessary in more severe cases of myocarditis[27]. Swedish sports medicine experts are adamant that exercise should be avoided whenever myocarditis is suspected[28]. So the message is clear, no vigorous exercise while working on getting rid of the inflammation. A couple of leisurely walks each day is probably OK and should be enough to ensure adequate bowel movement for the 4-6 weeks it will take to overcome the inflammation. Avoidance of excessive emotional or work-related stress is also mandatory during the recovery period.

Bacterial, viral and fungal infections are potent triggers of inflammation. Both myocarditis (inflammation in the heart associated with LAF) and atherosclerosis have been linked to an infection with the *Chlamydia pneumonaie* bacterium[29-31]. Some researchers have reported the presence of *Helicobacter pylori* bacteria in atherosclerotic lesions, but the evidence of a causative link is not as convincing as for *C. pneumonaie*[32]. There is also some evidence that a systemic *Candida albicans* infection can promote inflammation of the heart tissue (myocarditis) in severely immuno-compromised AIDS patients[33]. Just recently American researchers reported that mice infected with the coxsackievirus (associated with the common cold, meningitis and encephalitis) or the cytomegalovirus (associated with mononucleosis, hepatitis and colitis) developed myocarditis within 2 weeks of becoming infected[34]. Adding this evidence to Dr. Frustaci's findings[9,13] it is clear that there is an association between bacterial, viral and fungal infections and the development of myocarditis and, furthermore, that there is an association between myocarditis and heart arrhythmias (both atrial and ventricular). So if you have LAF it would seem prudent to undergo testing for possible infections and follow-up with medical treatment to eradicate them as necessary.

Diet can also be a potent source of inflammation. In some people wheat, dairy products and certain foods of the nightshade family (potatoes, peppers, eggplant, tomatoes) can cause a chronic inflammation[35]. I have found Dr. Peter D'Adamo's book "Eat Right for Your Type" particularly helpful in sorting out what to avoid and what to emphasize in the diet[35].

Elimination of Persistent Inflammation

If the inflammation persists after eliminating the causes as discussed in the previous section it is likely that it is due to an immune system dysfunction. There are several ways of correcting this.

It is evident from Dr. Frustaci's work that the inflammation (myocarditis) associated with LAF can be eliminated by treatment with prednisone[9]. Unfortunately, rather high dosages are required, at least initially. Prednisone has the potential for serious adverse reactions and its use is generally not recommended for extended periods of time. Dr. Frustaci used 1 mg per kg bodyweight per day for 4 weeks tapered to 0.33 mg for 4 months. So while prednisone may do

the job, at least if the inflammation is active, the overall benefit/risk ratio is not encouraging although probably no worse than that of long-term amiodarone (Cordarone) treatment.

An unfavourable benefit/risk ratio also applies to the use of aspirin and other NSAIDs to combat inflammation. They do not get at the root cause of the inflammation and can cause serious bleeding complications.

The cholesterol-lowering drug pravastatin (Pravachol) is effective in reducing the level of the inflammation marker C-reactive protein (CRP)[36]. This could benefit patients with atherosclerosis or rheumatoid arthritis, but as far as I know no work has been done to investigate the use of pravastatin in lone atrial fibrillation. Unfortunately, pravastatin has many potentially serious side effects including liver dysfunction, myopathy, rhabdomylosis, and possibly cancer. Pravastatin has also been found to lower coenzyme Q10 levels possibly leading to impaired cardiac function and congestive heart failure[37].

Human growth hormone replacement is another possible route for combating inflammation. Researchers at the Harvard Medical School recently reported that levels of IL-6 (interleukin-6) and CRP were both significantly reduced by the administration of recombinant human growth hormone in men with adult-onset growth hormone deficiency. The reduction in CRP level (30%) was similar to that obtained with pravastatin. IL-6 levels decreased by almost 40% as compared to the placebo group. The researchers conclude that, "long-term growth hormone replacement in men reduces levels of inflammatory cardiovascular risk markers" (IL-6 and CRP)[38].

Balancing the Immune System

Lymphocytes, a specialized kind of white blood cells, are important components of the immune system. They can be subdivided into B-lymphocytes, which produce antibodies, and T-lymphocytes (helper T-cells), which help identify foreign cells and antigens so that killer cells can dispose of them. T-cells come in two varieties, TH1 cells and TH2 cells. TH1 cells produce lymphokines that enhance the ability of the immune system to kill viruses, bacteria, fungi, and parasites. TH2 cells are involved in allergic reactions and release interleukin-6, a powerful marker of inflammation. A healthy immune system has an optimum balance of TH1 and TH2 cells. The results of too many TH2 cells are autoimmune diseases, allergies, inflammation and pain, while not enough TH1 cells can lead to cancer and infectious diseases[39].

Extensive research carried out at the University of Stellenbosch in South Africa has shown that a proprietary mixture of plant sterols and sterolins (Moducare) is very effective in increasing TH1 cell production (the "good" T cells) and decreasing TH2 cell production (the "bad" T cells). Moducare also normalizes the ratio between DHEA and cortisol[39]. Moducare has strong anti-inflammatory effects and sharply reduces IL-6 production. It has been found useful in the treatment of chronic viral infections, tuberculosis, and HIV infection[40]. Also it has been found to reduce the inflammatory response associated with excessive physical exertion[41]. The recommended dosage of Moducare is two capsules one hour before the main meals for the first month and then one capsule one hour before breakfast, lunch and dinner.

Alternative Approaches

Besides Moducare there are several other natural remedies that may be beneficial in reducing excessive inflammation. None of these remedies have been evaluated specifically for the inflammation involved in LAF or even atherosclerosis, but they have been found useful in the treatment of other inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.

- **Boswellia** (*Boswellia serrata*, Frankincense) - This resin obtained from the Boswellia serrata tree has been used as an anti-inflammatory in Ayurvedic medicine for centuries. Recent research has found it to be highly effective in the treatment of ulcerative colitis,

Crohn's disease and asthma[42-44].

- **Curcumin** – The yellow pigment of turmeric is as effective as cortisone in combating acute inflammation[45,46]. The recommended dosage is 400 mg three times daily preferably on an empty stomach[45].

- **Bromelain** – A mixture of enzymes found in pineapple has been found effective in the treatment of rheumatoid arthritis[45,47]. The recommended dosage is 250-750 mg/day[45].

- **Ginger** (*Zingiber officinalis*) – It is a strong antioxidant that inhibits the formation of inflammatory compounds. It has been found highly useful in the treatment of rheumatoid arthritis[45,48]. The recommended dosage (fresh ginger root) is 8-10 grams/day[45].

- **Sarsaparilla** (*Smilax sarsaparilla*) – This herb contains natural steroids and has been used since the Middle Ages in the treatment of rheumatism. It is also said to be useful in the treatment of mercury poisoning[49]. More recent animal experiments have shown it to be highly effective in the treatment of inflammation[50]. Sarsaparilla is also used as a blood purifier and the recommended dosage for this purpose is 250 mg three times daily of a 4:1 solid extract, or 1-4 grams three times daily of the dried root in the form of a decoction[166].

- **Omega-3 fatty acids** – Fish oils have been found beneficial in reducing rheumatoid arthritis symptoms[45,51,52]. The recommended daily dosage is 1.8 grams of eicosapentaenoic acid (EPA) from fish oil[45].

- **Pancreatic enzymes** – These have been found to be beneficial in the treatment of chronic inflammatory conditions such as rheumatoid arthritis[53]. They should be taken before meals.

- **Probiotics** – A recent review of the benefits of probiotics (*Lactobacillus* and *Bifidobacterium*) concluded that the modification of gut microflora by probiotic therapy might help alleviate inflammatory diseases such as arthritis and inflammatory bowel disease[54].

- **Antioxidants** – Last, but certainly not least, it is very important to ensure an adequate daily intake of the major antioxidants (vitamin C, vitamin E, selenium, beta-carotene, proanthocyanidins and alpha-lipoic acid). They all help to combat oxidative stress, a potent source of inflammation.

Conclusion

There is evidence that patients with atrial fibrillation may suffer from an inflammation as indicated by substantially higher than normal CRP levels. It would also appear that the higher the CRP levels are the more persistent and resistant to cardioversion is the AF. It is not clear from the research whether the inflammation causes the AF or whether AF causes inflammation; however, my guess would be that inflammation is a major cause of AF including LAF.

It is, perhaps unfortunately, also clear that inflammation is not the sole cause of AF. Dr. Frustaci only observed inflammation in 67% of the LAF patients who underwent biopsies. Dr. Mina Chung of the Cleveland Clinic, the lead author of their study, informed me that most, but not all AF patients involved had abnormally high CRP levels[55].

I personally do not have an inflammation. During a recent LAF episode my CRP level was 0.03 mg/dL – well within the normal range. I had been on an anti-inflammatory protocol since August 2001 so I cannot say for certain whether I ever had an inflammation, but I am convinced that I don't have one now – especially since my sedimentation rate is at the very low end of normal as well.

Very few afibbers have had their CRP level tested so we have not, from our surveys, been able to ascertain whether high CRP levels are common or not. It may well be worthwhile to include a CRP test in your next physical examination, or preferably during or shortly after an episode. If it is high then it would make sense to try to reduce it, especially since a high CRP level is also a risk factor for stroke and heart attack. I believe natural supplements such as Moducare, MSM (methyl sulfonyl methane), curcumin (with piperine), bromelain, probiotics (acidophilus and yogurt), and pancreatic enzymes may be useful in reducing inflammation. Lowering CRP levels (reducing inflammation) would be particularly important for afibbers planning on undergoing a cardioversion.

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