Editorial

Oxidative stress is believed, by many researchers, to be the root cause of such diverse diseases as cancer, cardiovascular disease, arthritis, cataracts, and inflammatory bowel disease. Oxidative stress occurs when the body’s antioxidant defenses are inadequate to cope with the attacks from free radicals to which it is exposed.

Could atrial fibrillation and, in particular, lone atrial fibrillation also be caused by oxidative stress? I believe that in many cases, but perhaps not all, the answer is yes. In this issue I discuss the evidence for a possible connection and also suggest a couple of supplements that may be useful in preventing oxidative stress.

One thing that can really get me “hot under the collar” is when I hear and read about afibbers, in particular vagal afibbers, still being prescribed digoxin. In the article “Digoxin: The Medicine from Hell” I explain why afibbers should never take digoxin.

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Yours in health and sinus rhythm,
Hans Larsen

The Oxygen Connection

There is growing evidence that idiopathic (lone) atrial fibrillation is caused by a combination of an inflamed heart lining and a dysfunctional autonomic nervous system[1-7]. Many of the triggers for atrial fibrillation such as mental and physical stress, vigorous exercise, alcohol consumption, mercury poisoning, bacterial, viral and fungal infections, and oxidative stress have been identified as potential initiators of inflammation[8-13]. There is also a distinct association between autonomic nervous system dysfunction and the inflammatory response[14,15].

Mapping of fibrillating atria has shown that ectopic (premature) beats and fibrillation itself originate in clearly discernible agglomerations of individual heart cells that are beating to their own rhythm rather than to the rhythm generated in the SA (sino-atrial) node. It is thought that these agglomerations are actually inflamed heart tissue and that atrial fibrillation originates here and is sustained by scar tissue (fibrosis) generated by previous inflammations[1-5].
It is also clear that the junctions between the left atrium and the pulmonary veins are the most common locations for these “rogue”, inflamed cell agglomerations. Radio Frequency Ablation and, in particular, Circumferential Ultrasound Vein Ablation have both been found effective in stopping atrial fibrillation episodes permanently by creating a scar tissue around the inside circumference of the pulmonary veins and thus preventing any aberrant electrical impulses from entering the heart itself.

Late last year German researchers reported that most intermittent atrial fibrillation episodes are preceded by a series of atrial premature complexes (APCs). They also found that 77.5% of these complexes originated in the left atrium while only 2% originated in the right atrium; the origin of the remaining APCs could not be determined[16]. Thus the left atrium and particularly the junctions with the pulmonary veins are, by far, the most common origins of the APCs that set off atrial fibrillation episodes.

What, apart from size, is different between the left and right atrium or for that matter, between the junctions of the left atrium and the pulmonary veins and the junctions of the right atrium and the venae cavae?

In a nutshell, oxygen concentration (partial pressure) and shear stress. The blood returning to the right atrium is relatively low in oxygen content and flows fairly sedately through the venae cavae into the heart. The blood flowing from the lungs to the left atrium, on the other hand, is highly oxygenated and flows more forcefully through the pulmonary veins thus generating a significant amount of shear stress especially at the junctions with the left atrium.

The combination of a high oxygen pressure and shear stress is a potent breeding ground for reactive oxygen species (ROS). The superoxide anion, singlet oxygen, nitrogen dioxide (peroxynitrite) and hydroxyl radicals are all members of the ROS family. They share the dubious distinction of being able to cause inflammation and inflict considerable damage in tissues, cells and individual DNA strands.

One would expect vigorous exercise to markedly increase oxygen concentration and shear stress and thus promote the formation of ROS. Indeed there is evidence that orienteering, marathon running, and cross-country skiing are associated with an increased incidence of arrhythmias and asthma[17-19]. Finnish researchers found that middle-aged, elite orienteers had a 5 times higher incidence of lone atrial fibrillation than did the general population[17]. Breathing air polluted with nitrogen dioxide has also been found to increase the incidence of inflammation and arrhythmias[20-22]. Other forms of air pollution (particulate matter) has been linked to the formation (in the lungs) of inflammatory cytokines that are released into the blood circulation[23].

Under normal circumstances any ROS attacking the heart lining or adjacent lung tissue would quickly be rendered harmless by the body’s own antioxidants or by antioxidants obtained through the diet. However, if antioxidant defenses are inadequate, the immune system is compromised or if the autonomic nervous system is highly dysfunctional or stressed it is likely that the ROS could get the upper hand and initiate an inflammatory response and subsequent arrhythmia. One way to avoid this response would be to increase the supply of antioxidants with the ability to neutralize (quench) nitrogen dioxide, singlet oxygen and other ROS before they can do any damage to vulnerable tissue. Fortunately, there are two dietary antioxidants, gamma-tocopherol and lycopene, that are highly effective in neutralizing reactive oxygen species.

**Gamma-tocopherol**

Gamma-tocopherol is a member of the vitamin E family, which also encompasses alpha-tocopherol, beta-tocopherol, delta-tocopherol, and 4 different tocotrienols. Gamma-tocopherol is the main form of vitamin E in the diet while alpha-tocopherol is the most abundant form in human blood and tissue. Until quite recently gamma-tocopherol was thought to be of little importance. Laboratory experiments using rats had shown that gamma concentrations in blood and tissues were insignificant compared to the levels of alpha. This lead to the conclusion that the active form of vitamin E was alpha-tocopherol and future research therefore concentrated on this compound. It is worth noting that alpha-tocopherol is usually the sole component in vitamin E supplements.
In 1998 researchers at the Canadian National Research Council concluded that when it comes to gamma-tocopherol people are not rats. They found that blood and tissue levels of gamma in humans are far higher than the rat experiments had indicated. Particularly noteworthy is the finding that gamma-tocopherol constitutes as much as 30 to 50% of the total vitamin E content of human skin, muscles, veins and fat (adipose) tissue\[24,25\]. There is also evidence that gamma is exceptionally important in protecting lung tissue\[21,26,27\].

Research has shown that gamma-tocopherol is superior to alpha when it comes to trapping reactive nitrogen dioxide specimens and preventing lipid peroxidation under oxidative stress\[25-28\]. The gamma form of vitamin E is also less likely to act as a prooxidant than is alpha-tocopherol\[25\]. As if this was not enough, gamma-tocopherol also helps prevent cardiovascular disease, prostate cancer, lung inflammation, and perhaps type 1 diabetes and has potent anti-inflammatory properties\[25,26,29\].

As mentioned previously, gamma-tocopherol is the main form of vitamin E in the diet and accounts for about 70% of the total dietary vitamin E intake with the main sources being nuts, seeds, and vegetable oils\[27\]. Unfortunately, studies have shown that between 25 and 40% of all Americans are deficient in vitamin E\[30\]. The realization that the daily diet cannot provide an adequate intake of vitamin E has lead many people to supplement with vitamin E or rather, alpha-tocopherol. Unfortunately, ingesting large amounts of alpha-tocopherol has a disastrous effect on gamma levels\[26,31\]. Researchers at the University of California found that supplementing for one year with 800 mg/day of synthetic alpha-tocopherol resulted in a dramatic drop in gamma levels in both blood plasma and adipose tissue. The plasma concentration of alpha more than doubled within 2 weeks of starting supplementation and remained elevated for the remainder of the supplementation period. Gamma-tocopherol levels in adipose tissue, however, declined by more than 70% by the end of the supplementation period and the gamma/alpha ratio in adipose tissue decreased by almost 200%. Of equal concern is the finding that it took as long as 5 years for gamma levels to return to normal after the alpha-tocopherol supplementation was stopped\[31\].

Thus it is conceivable that a large proportion of the population is deficient in gamma-tocopherol, especially if they are supplementing with alpha-tocopherol. Could this deficiency impair the body’s antioxidant defenses to the point where reactive oxygen species get the upper hand and cause inflammation in the lungs or myocardium ultimately resulting in asthma or atrial fibrillation?

Clearly, extensive epidemiological studies and clinical trials would be required to determine this. However, in the meantime, I have personally switched to a mixed vitamin E supplement containing mostly gamma-tocopherol. I believe it is important to take both gamma- and alpha-tocopherol so as not to disturb their natural ratio in the body; however, after having supplemented with 400 IU/day of alpha since 1967 I am sure my gamma levels need a significant boost.

**Lycopene**

Lycopene is a member of the carotenoid family and has over 500 relatives. Carotenoids are yellow-to-red pigments found in all green plant tissues and in some species of algae. So far 21 different carotenoids have been found in human blood\[32\]. The most abundant ones are alpha-carotene, beta-carotene, lutein, lycopene, cryptoxanthin and zeaxanthin. These 6 carotenoids are all antioxidants. They are very effective in neutralizing (quenching) a highly reactive form of oxygen called singlet oxygen but also, to some extent, act to break up the chain reactions involved in lipid peroxidation (a precursor of atherosclerosis)\[33-37\]. Lycopene is the most abundant carotene in the human body and is, by far, the most effective quencher of singlet oxygen – more than twice as effective as beta-carotene\[35,38-42\]. Beta-carotene, however, is the most abundant carotenoid in vegetables and has long been thought of as being mainly responsible for the protective effects of vegetables against cancer and heart disease.

Recent research has discovered that lycopene may be at least as important as beta-carotene for human health. Finnish researchers have found that middle-aged men with low lycopene levels have a 3-fold high risk of suffering a heart attack or stroke than do men with higher levels\[43,44\]. There is also increasing
Evidence that lycopene and its main dietary source, tomatoes and tomato products, are highly protective against prostate cancer[45,46].

More relevant to our quest though is the fact that lycopene is the most effective neutralizer of singlet oxygen among all known antioxidants and is also highly effective in dealing with nitrogen dioxide[38-42,47-49].

In a situation similar to that existing between alpha- and gamma-tocopherol, beta-carotene has long been the “favourite” and is included in most multivitamins in relatively large amounts. Lycopene, on the other hand, is rarely included in multivitamin supplements. The average dietary intake of beta-carotene is somewhere between 2 and 5 mg/day. Some supplements contain 10 times this amount and can increase the beta-carotene level in the blood by a factor or 10. Little is know about the effect of such abnormally high levels, but they could conceivably be toxic over the long term and almost certainly will cause serious imbalances in the concentration of other important carotenes[50,51].

It is of particular interest that beta-carotene shows its greatest activity as an antioxidant at low partial pressures (tension) of oxygen such as found in blood vessels and most inner organs of the body[33,34]. It is not effective at higher oxygen tensions such as would be found in the lungs. Some researchers believe that beta-carotene acts as a prooxidant at higher oxygen tensions[33,51]. This effect is especially strong at high beta-carotene concentrations[33]. In other words, a high intake of beta-carotene might increase oxidative stress at points of high oxygen concentrations such as encountered at the junction between the pulmonary veins and the left atrium.

Of equal concern is the fact that a high intake of beta-carotene in isolation markedly lowers the concentration of lycopene in the blood; this effect is particularly significant in the case of synthetic beta-carotene[37,52]. Since lycopene is the most active fat-soluble antioxidant in human blood (even more active than vitamin E), a reduction of 25% or more in its concentration could have serious consequences. It is worth noting that at least one experiment has shown that supplements containing beta-carotene from natural sources do not cause a statistically significant drop in lycopene concentration[37]. Since most multivitamin supplements contain synthetic beta-carotene, which suppresses lycopene absorption, it is quite possible that a significant proportion of the population is deficient in lycopene, a very efficient neutralizer of reactive oxygen species. It is also conceivable that this deficiency may impair the body’s antioxidant defenses to the point where excessive oxidative stress and subsequent inflammation and atrial fibrillation can develop. Epidemiological studies and clinical trials care clearly required to support or discard this hypothesis. However, in the meantime, I have personally switched to a multivitamin that contains natural beta-carotene and have also added 20 mg of lycopene to my daily vitamin regimen.

Conclusion
There is growing evidence that lone atrial fibrillation is caused by a combination of an inflammation of the heart lining and a dysfunctional autonomic system. I propose that excessive oxidative stress, caused by reactive oxygen species, at the upper part of the left atrium could be a major cause of ectopic (premature) beats and subsequent atrial fibrillation episodes. If this is indeed the case, then supplementation with the two most effective dietary neutralizers of reactive oxygen species, gamma-tocopherol and lycopene, may prove beneficial in reducing the frequency of fibrillation episodes.

References
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Digoxin: The Medicine from Hell?

Digoxin (digitalis, Lanoxin), originally derived from the foxglove plant, has been in use for 200 years as a heart medication. The primary indication for digoxin is in the treatment of heart failure (congestive heart failure) especially if accompanied by atrial fibrillation. From this original application digoxin has expanded into the treatment of atrial fibrillation and lone atrial fibrillation. Most medical textbooks still laud digoxin as an effective drug for heart failure. Does it actually work?

The Digitalis Investigation Group, a large team of American and Canadian researchers released a major report, which presents the findings of a large, randomized, double-blind, placebo-controlled trial of digoxin in the treatment of heart failure patients. The three-year trial involved over 7000 patients with heart failure (left ventricular ejection fraction less than 0.45). The patients were divided randomly into two equal-sized groups with one group receiving 0.250 mg of digoxin per day and the other group receiving a placebo; all
patients in both groups continued on ACE inhibitors and diuretics. The average follow-up time was 37 months. At the end of the trial 35% of the participants had died in each group. The death rate attributable to worsening heart failure was slightly less in the digoxin group, but the number of deaths from other cardiovascular events such as arrhythmias and strokes was higher. Patients on digoxin were less likely to be admitted to hospital for worsening heart failure (26.8 versus 34.7% for controls), but had higher admission rates for suspected digoxin toxicity (2.0 versus 0.9%).

The researchers conclude that digoxin does not reduce the risk of death from heart failure or other causes, but that it does reduce the rate of hospital admissions, especially for worsening heart failure. In other words, while digoxin may, to some extent, ameliorate the symptoms of heart failure it does not reverse or cure it nor does it reduce the risk of death from this condition[1,2].

British researchers followed 484 heart failure patients for three years and found that the mortality among those taking digoxin was 38.9% as compared to only 21.3% among controls. The researchers conclude that the use of digoxin in heart failure patients is associated with an adverse prognosis and suggest that beta-blockers and spironolactone may be a better choice for ameliorating the symptoms of heart failure[3].

Toxicity and Interactions
The “therapeutic window” for digoxin is very narrow. Most patients are started on a daily dosage of 0.250 mg/day; however, this is often too little for some patients and too much for others. Very careful evaluation is required in order to find just the right dosage. Unfortunately, this is rarely done in actual practice.

Researchers at the Health Care Department in Maryland found that in the period 1985 through 1991 over 200,000 of 3.3 million digitalis users were hospitalised because of digitalis intoxication. It is ironic that digitalis is often prescribed for people who suffer from atrial fibrillation and yet, the most common manifestation of digitalis intoxication is also atrial fibrillation. Other symptoms of digitalis poisoning are nausea, vomiting, diarrhea, psychoses, and fatigue. Perhaps the most disturbing finding in the study is that in 73% of all cases the reason for prescribing the digitalis in the first place was unclear or weak. The researchers also point out that the high level of hospitalisation for adverse effects of digitalis is, to a large extent, due to inadequate monitoring of patients taking the drug. It is also of concern that for the period in which the researchers uncovered data for the 200,000 hospitalizations only 577 adverse events involving digitalis were reported directly to the FDA by doctors or hospitals[4].

Other researchers have noted that digoxin is often prescribed seemingly for no good reason. Dr. Wilbert Aronow of the Mount Sinai School of Medicine found that 19% of patients admitted to a nursing home had been prescribed digoxin. A thorough medical examination and evaluation concluded that 47% of these patients should not be taking digoxin at all. Dr. Aronow also noted that 18% of the patients receiving digoxin had been misdiagnosed as having congestive heart failure when, in fact, they were suffering from edema or dyspnea (laboured breathing). Digoxin therapy was safely discontinued in the 47% of the patients for whom it had been inappropriately prescribed[5].

Not only is digoxin highly toxic, but it can also interact with herbs such as Siberian ginseng and with antiarrhythmic medications such as flecainide (Tambocor), propafenone (Rythmol), and amiodarone (Cordarone)[6-8]. These drugs all increase blood levels of digoxin thus making a toxic reaction even more likely unless digoxin dosage is adjusted[7,8].

Digoxin and Atrial Fibrillation
Digoxin is still routinely prescribed for patients with atrial fibrillation even though there is no evidence that it is beneficial and growing evidence that it may actually be harmful. Digoxin does not convert atrial fibrillation to sinus rhythm[8,9]. Its ability to slow the heart rate during an atrial fibrillation episode is doubtful[10] and there is no evidence that it prevents future episodes of paroxysmal atrial fibrillation[11,12]. Dr. Rodney Falk, MD of the Boston School of Medicine sums it up, “Digoxin is probably not of value for preventing tachycardia (rapid heart beat) at the onset of paroxysmal atrial fibrillation and its use as sole agent for this indication, although widespread, has no basis”[11].
Not only is digoxin useless in the prevention and treatment of atrial fibrillation it can actually be detrimental. Dr. Philippe Coumel, MD head of the cardiology section of the Hopital Lariboisiere in Paris says, “Not only are beta-blockers or digoxin not indicated in vagal atrial fibrillation, but they are definitely contraindicated as they tend to promote the arrhythmia and may block the action of conventional antiarrhythmic treatment”[13]. Dr. Coumel’s statement has been endorsed by the American Heart Association[14].

Researchers at the University of Michigan Medical Center go even further in their condemnation of digoxin. Their conclusion from a recent clinical trial, “The results of the present study suggest that digoxin may facilitate or promote early recurrences of atrial fibrillation after conversion to sinus rhythm not only in patients with vagotonic (vagal) atrial fibrillation, but also among the general population of patients with atrial fibrillation”[15]. It is now also clear that digoxin may not only prolong the duration of episodes, but may actually convert the paroxysmal (intermittent) form to the chronic form[16].

As if this is not enough, researchers have also found that digoxin can cause visual problems even at dosages normally considered safe and may significantly aggravate asthma symptoms[17,18].

Yes, digoxin may truly be the medicine from hell and it certainly should never be used by people with lone atrial fibrillation. If a medicine is needed for the control of heart rate then calcium channel blockers such as verapamil or diltiazem or beta-blockers like atenolol or metoprolol would be a better choice – except for vagal afibbers who should not take beta-blockers.

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Lone atrial fibrillation is common. Spanish researchers report that lone atrial fibrillation is more common than generally thought. They carefully examined 300 patients with paroxysmal atrial fibrillation admitted to 11 hospitals in Catalonia. LAF was diagnosed in 22.3% of the cases. Systemic hypertension was found in 33.7%, coronary heart disease in 9.7%, and mitral or aortic valve disease in 12%. LAF patients tended to be younger than patients with hypertension or heart disease and were less likely to suffer from dyspnea (laboured breathing).


Stroke risk greater in chronic afibbers. Italian researchers report that younger people with paroxysmal (intermittent) lone atrial fibrillation have a low risk of stroke while older people with chronic afib have a significantly higher risk (1.3% per year). Cardiologists at the Georgetown University Medical Center comment that the higher risk of stroke among older patients with chronic afib may be related to an enlarged left atrium. They conclude that anticoagulation with warfarin should be considered in these patients, however, they also state, “Patients younger than 60 to 65 years with paroxysmal lone atrial fibrillation and no clinical or echocardiographic risk factors for thromboembolism do not warrant therapy with warfarin – their risk of stroke is probably less than the likelihood of a significant bleed”.


Dizziness in atrial fibrillation. Many afibbers are familiar with the dizziness that can accompany the beginning of an afib episode. Dutch researchers now report that there is a clear association between the severity of the dizziness and the degree of impairment of the autonomic nervous system. They suggest that being on antiarrhythmic drugs to prevent episodes may actually worsen the dizziness when another episode does occur. Beta-blockers, on the other hand, may diminish the dizziness as may physical training designed to improve autonomic function.