

THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation!

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8th YEAR



Judi and I shall be away on vacation at the time the September issue is usually published, so we decided to publish it now so as to give you lots of fascinating summer reading. It is a banner issue with another very interesting afib reduction/elimination protocol found effective by a 47-year-old male mixed afibber.

Some of the highlights from our review of current medical journals are:

- *Gender differences in arrhythmia presentation and treatment are very real as are the differences in the effect of a daily aspirin.*
- *An exciting array of new drugs is vying to replace warfarin – and not a moment too soon!*
- *Spanish researchers have confirmed that long-term, vigorous endurance exercise increases the risk of developing afib, and Italian researchers add that so does stress and excessive coffee consumption.*
- *On the ablation front, the first evaluation of the Hansen Sensei robotic ablation system, avoidance of atrioesophageal fistula, and the latest survey of the rate of major complications associated with pulmonary vein ablation.*

Finally, if you need to restock your supplements, please remember that by ordering through my on-line vitamin store you will be helping to defray the cost of maintaining the web site and bulletin board. You can find the store at <http://www.afibbers.org/vitamins.htm> - your continuing support is truly appreciated.

Hope you are enjoying a great summer with lots of NSR,

Hans

Highlights

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Gender differences in aspirin effectiveness

UTRECHT, THE NETHERLANDS. Aspirin has been found effective in the prevention of heart attack (myocardial infarction), ischemic stroke, and cardiovascular death in patients who have already

experienced a heart attack or stroke. Its benefits in primary prevention, that is in the prevention of a first heart attack or stroke, are much less clear. Researchers at the University Medical Center in Utrecht have just published a major study aimed at determining the benefits and risks of taking a daily aspirin for primary prevention of cardiovascular events. Taking into account all major studies on the subject as well as discharge statistics from Dutch hospitals, the researchers developed a computer model for predicting the risk of a first heart attack, ischemic stroke, hemorrhagic stroke, major gastrointestinal bleeding, and death in four specific age groups of men and women who were, or were not, taking aspirin on a daily basis.

Using a 55-year-old man with no cardiovascular risk factors as an example, they found an annual incidence of a first heart attack to be 0.40%/year with no aspirin and 0.28%/year with daily aspirin, or a relative risk decrease of 30%. There was no

decrease in risk of a first ischemic stroke, but the relative risk increase of a first hemorrhagic stroke was 42%, and that of major gastrointestinal bleeding 42%. The daily aspirin did not prevent a first heart attack in 55-year-old women, but did reduce the risk of ischemic stroke from 0.07%/year to 0.05%/year, or a relative risk reduction of 24%. However, this benefit was offset by a relative risk increase of hemorrhagic stroke of 5% and of major gastrointestinal bleeding of 70%.

Overall, the researchers concluded that the risk involved in the daily aspirin ritual outweighs the benefit in healthy 55-year-old women. A healthy 55-year-old man may gain 3 days of "Quality Adjusted Life Years" (QALY) over a 10-year period by taking aspirin on a daily basis.

The net benefits of daily aspirin usage increased with increasing age and the presence of cardiovascular risk factors. For healthy men, the gain in QALY over a 10-year period was 9 days at age 65 years and 15 days at age 75 years. Corresponding numbers for women were a loss of one day at age 65 years and a gain of 6 days at age 75. However, for men with 5 times normal cardiovascular risk the net gain in QALY over a 10-year period was 34 days at age 55, 68 days at age 65, and 108 days at age 75. Corresponding

numbers for women were 2 days, 12 days, and 38 days.

The researchers conclude that for most women aspirin treatment results in increased health care costs and worse health outcomes. However, for women 65 years or older with 5-times-increased cardiovascular risk, aspirin may have a favourable benefit/risk ratio. The benefits for healthy men are not impressive until age 75, but daily aspirin would generally seem to be beneficial for men with moderate or high risk for cardiovascular disease.

Greving, JP, et al. Cost-effectiveness of aspirin treatment in the primary prevention of cardiovascular disease events in subgroups based on age, gender, and varying cardiovascular risk. Circulation, Vol. 117, June 3, 2008, pp. 2875-83

Mosca, L. Aspirin chemoprevention – one size does not fit all. Circulation, Vol. 117, June 3, 2008, pp. 2844-46

Editor's comment: The major "take-home" message from this study is that one size does definitely not fit all when it comes to using aspirin for prevention of a first cardiovascular event. In general, aspirin may benefit men with a 10-year cardiovascular disease risk greater than 10% and women with a 10-year cardiovascular disease risk greater than 15%.

New Chinese medicine-based antiarrhythmic

HONG KONG, CHINA. The contraction (depolarization) and resting (repolarization) periods of the heart cells are determined by the balance of the inward flow of calcium ions and the outward flow of potassium (K) ions. The major outward K currents are I_{Kur} (ultra-rapid delayed rectified K⁺ current) and I_{to} (transient outward K⁺ current). The Class III antiarrhythmics (amiodarone, sotalol and dobutilide) work by blocking the outward K⁺ currents so as to increase the resting period (ERP) during which afib cannot be initiated. Ideally, only the K⁺ currents in the atria would be blocked since blocking them in the ventricles can lead to arrhythmias (proarrhythmic effects) and lengthening of the corrected QT interval (long-QT syndrome). I_{Kur} is only present in the atria, so a drug that would block only I_{Kur} would be a highly desirable antiarrhythmic.

Researchers at the University of Hong Kong now report that they may have found such a "drug" in the natural flavone, acacetin, derived from the

traditional Chinese medicine *Xuelianhua*. Their experiments, so far, have only involved human heart cells and various animals, but are intriguing nevertheless. The researchers found that acacetin is non-toxic even when administered in relatively large doses. They also observed that it does not prolong the corrected QT interval in isolated rabbit hearts. Most importantly, they found that acacetin was highly effective in blocking both I_{Kur} and I_{to} , prolonged the atrial effective resting period (AERP), and prevented the induction of atrial fibrillation in dogs. As an added bonus, acacetin was also found to block the I_{Kach} (acetylcholine-activated K⁺ current), which may be instrumental in the initiation of vagally-induced afib.

Other research has shown that acacetin has anti-inflammatory effects, is an effective antioxidant, and exhibits anti-cancer effects in human prostate and lung cancer – truly a "super drug". The Chinese researchers conclude that oral acacetin is a

promising agent for the prevention and treatment of atrial fibrillation.

Li, GR, et al. Acacetin, a natural flavone, selectively inhibits human atrial repolarization potassium currents and prevents atrial fibrillation in dogs. Circulation, Vol. 117, May 13, 2008, pp. 2449-57

Editor's comment: I usually do not report on cell culture and animal experiments since there is a distinct possibility that their results may not apply to

humans. Nevertheless, I found the results of this study so fascinating that I decided to make an exception. As far as I know, acacetin is not available outside the laboratory, but *Xuelianhua* might be. Of course, there is no way of knowing whether this whole botanical medicine may have similar effects to the highly concentrated extract acacetin.

AF and long-term endurance sports practice

BARCELONA. SPAIN. Several studies have concluded that long-term participation in vigorous, sustained exercise (sports) increases the risk of developing lone atrial fibrillation (LAF). A group of Spanish researchers now confirm this connection. Their study included 183 male marathon runners (between the ages of 20 and 60 years) who had participated in the 1990 Barcelona marathon and joined the study between 1990 and 1992. The annual incidence of LAF in this group was compared to the incidence in a group of 290 largely sedentary men recruited from a general population study conducted in 1994-96.

The two groups were followed for 12 years and 6 years respectively. At the end of the follow-up period, 9 of the marathon runners and 2 of the control subjects had developed LAF. This corresponds to an annual incidence of 0.43% among the athletes as compared to 0.11% among the sedentary men.

The researchers conclude that the overall incidence of LAF among marathon runners is still relatively low at less than 0.5%/year, but distinctively higher than the incidence associated with a more sedentary lifestyle. The only statistically significant difference between athletes who developed afib and

those who did not was a larger inferosuperior left atrial diameter in the afibbers. However, as the measurement of atrial dimensions was done after the diagnosis of LAF, it is not clear whether the enlargement helped precipitate the atrial fibrillation, or the atrial fibrillation caused the enlargement.

Molina, L, et al. Long-term endurance sport practice increases the incidence of lone atrial fibrillation in men: a follow-up study. Europace, Vol. 10, 2008, pp. 618-23

Editor's comment: There would seem to be little doubt now that long-term, vigorous endurance exercise is a risk factor for the development of LAF. Whether a risk increase of 0.3%/year over that of sedentary men is acceptable is clearly a decision to be made by each athlete. Unfortunately, it is unlikely that endurance athletes worry about developing LAF until it is too late. It is interesting that the Spanish researchers use the following definition for LAF: "Lone atrial fibrillation is characterized by the presence of atrial fibrillation in the absence of structural heart disease or other identifiable causes of arrhythmia such as hypertension, hyperthyroidism, or alcohol use." This definition is actually more akin to the definition of idiopathic atrial fibrillation, i.e. afib with no known cause, but close to the definition we generally use.

Evaluation of Hansen Sensei robotic system

CLEVELAND, OHIO. The success of a pulmonary vein isolation (PVI) ablation depends on the location and quality of the lesions (burns) imparted during the procedure. Lesion quality, in turn, depends on such factors as catheter design, duration of burn, power (wattage) applied during the burn (for RF ablations), the pressure applied to the catheter during the burn, and last, but certainly not least, the stability of the catheter during the burn. The

ultimate aim of lesion creation is to form a barrier preventing the propagation of electrical impulses throughout the entire thickness of the heart wall – without penetrating the wall in the process (tamponade) – very exacting work indeed!

The process (mapping) used in determining the location of the lesion(s) may involve the determination of electrical potentials or the location

of anatomical features using electroanatomical (CARTO) mapping now increasingly associated with an overlay of a CT or MRI scan (CartoMerge). The actual ablation process is performed by the electrophysiologist (EP) who is standing next to the patient and manually directing a catheter, which extends from the femoral vein in the groin to the left atrium. Needless to say, this process takes great manual dexterity and experience and tends to produce very uneven results largely related to the skill of the EP.

Not surprisingly, a great deal of effort has been expended on coming up with ablation systems that will “level the playing field” by inserting a robot between the EP and the tip of the ablation catheter. Two such systems are now under evaluation. The **Stereotaxis system** uses a catheter with a magnetic head, which can be easily maneuvered to any location in the atria by controlling (remotely) the magnetic flux from 3 electromagnets placed to the right and left of the body (at heart level) and above the head. The **Hansen Sensei system** uses a robotic arm (placed next to the patient at groin level), which essentially guides a flexible sheath (tube) extending from the groin to the atria through the femoral vein. The ablation catheter is threaded through the sheath with only the tip (1 cm) extending from the sheath. The movement of the sheath can be very closely controlled by the robotic arm which, in turn, can be precisely controlled by the EP sitting at a remotely located console. Both systems have the great advantage of limiting radiation exposure to the operator by a factor of 10 or more.

A group of expert EPs (including Dr. Andrea Natale, Pr. Michel Haissaguerre, Pr. Pierre Jais, Dr. Walid Saliba, Dr. David Burkhardt, Dr. Vivek Reddy, Dr. Luigi Di Biase, et al) now report on the first full scale evaluation of the Hansen Sensei system. The study involved 40 atrial fibrillation patients of which 90% had lone atrial fibrillation. The patients were recruited at 3 centers (Bordeaux, Coburg and Prague); their average age was 57 years, and most (75%) had paroxysmal afib with the remaining 25%

having persistent afib. Twenty-three patients also had typical right atrial flutter. The patients (29 men and 11 women) underwent a pulmonary vein antrum isolation using CARTO mapping, ICE guidance, and the Hansen Sensei system. The 23 patients with flutter also underwent a right atrial flutter ablation. Total average procedure time for the afib ablation was about 3 hours with an ablation time of 106 minutes and fluoroscopy time of 83 minutes. The patients were followed for 12 months at which time 34 (85%) were free of any arrhythmia without antiarrhythmics, while 13% were free of arrhythmia while taking previously ineffective antiarrhythmics. There was one (2.5%) pericardial effusion associated with the use of the Hansen Sensei system.

The EPs conclude that the use of the robotic catheter remote control system for transseptal puncture and endocardial navigation and ablation is safe and feasible, and give results similar to those obtained by EPs using manual guidance. (Editor’s note: Only the very best EPs would obtain a 98% complete and partial success rate with just one ablation). NOTE: This study was supported by a grant from Hansen Medical, Inc.

Saliba, W, et al. Atrial fibrillation ablation using a robotic catheter remote control system. Journal of the American College of Cardiology, Vol. 51, June 24, 2008, pp. 2407-11

Callans, DJ. Can we improve upon human performance in the electrophysiology laboratory? Journal of the American College of Cardiology, Vol. 51, June 24, 2008, pp. 2412-13

Editor’s comment: This is indeed a very exciting study which, in contrast to other studies involving robotic guidance, actually presents long-term outcome results. It would seem that the Hansen Sensei system pretty well solves all the problems involved in creating “perfect” lesions except the one that besets all robotic systems – that of pressure control. However, work is apparently underway to develop a suitable pressure sensor that will hopefully solve this problem and perfectly emulate the pressure exerted by the hands of a skilled EP.

Complications in AF ablation

BALTIMORE, MARYLAND. Although the risk of dying during or after a RF ablation for atrial fibrillation is infinitesimally small, the risk of major complications is not negligible. A recent worldwide survey found a major complications rate of 6%,

while a just published Italian study found a rate of 3.9%. A study at the Cleveland Clinic (400 patients) found a moderate-to-severe stenosis rate of 0.25%, a stroke/TIA rate of 0.8%, and the risk of tamponade at 0.5% for a total major event rate of

1.6%. In contrast, an Austrian study involving only 75 patients found a serious adverse event rate of 12%.

Electrophysiologists at Johns Hopkins Hospital in Baltimore now report on their complication rate in a series of 517 patients treated for atrial fibrillation by RF ablation during the period 2001 to 2007. Up until January 2003 the segmental (Haissaguerre) procedure was used. It was replaced by the

circumferential (Pappone, CARTO) method and in March 2005 the CartoMerge system (combining CARTO and CT scan or MRI images) was added. The 517 patients underwent a total of 641 procedures (24% repeat rate). Overall success rate was not reported, but an earlier report from Johns Hopkins involving 200 patients gave the complete success rate as 28% after one procedure and 41% after multiple procedures. The most common major complications are listed below:

Stroke	7	1.1 %
Tamponade	8	1.2 %
Vascular injury	11	1.7 %
Pulmonary vein occlusion	1	0.2 %
Hemothorax	2	0.3 %
Heart block	1	0.2 %
Acute lung injury	1	0.2 %
Mitral valve injury	<u>1</u>	<u>0.1 %</u>
	32	5.0 %

The researchers found an overall major complication rate of 5.0%. The rate was higher (6.0%) for patients over the age of 70 years and for women (7.8%). They conclude that complication rates for AF ablation remain significant.

Spragg, DD, et al. Complications of catheter ablation for atrial fibrillation: incidence and predictors. Journal of Cardiovascular Electrophysiology, Vol. 19, June 2008, pp. 627-31

Atrioesophageal fistula avoidance

MAINZ, GERMANY. The accidental creation of a fistula (hole) between the back wall of the left atrium and the esophagus is a rare but often fatal complication of pulmonary vein ablation. In early 2005 it was estimated that about 20 cases had occurred worldwide which would correspond to an incidence of 0.05% or less. The creation of an atrioesophageal fistula would appear to be more common when using the circumferential (Pappone) ablation approach than when using the segmental (Haissaguerre/Natale) approach. Clearly, avoiding lesion creation in the part of the left atrium that abuts the esophagus would be an effective way of avoiding a fistula, but would doing so reduce the likelihood of the ablation being successful? A team of German researchers recently set out to answer this question.

Their clinical trial involved 43 paroxysmal afibbers (28 men, 15 women) with an average age of 62 years. Seventy percent of the patients had idiopathic afib (lone afib of no known cause). The study participants were divided into 2 groups. Group A underwent a standard segmental

pulmonary vein isolation (PVI) creating lesions to completely isolate (electrically) each pulmonary vein from the left atrium regardless of the anatomical relationship between the ablation sites and the esophagus. An average of 3.7 veins were successfully isolated and 67% of the patients had all veins completely isolated.

During the ablation of the remaining patients (Group B) special care was taken to avoid ablation over the esophagus (a stomach tube was inserted in the esophagus so that its location was clearly visible in fluoroscopy imaging). In Group B only 55% of the patients had all veins successfully isolated and the mean number of successfully isolated veins was 3.2. The study participants were followed up with ECGs and extended Holter monitoring for a minimum of 6 months. At the end of 3 months, 90% of patients in Group A and 95% of those in Group B were afib-free. Corresponding numbers at 6 months were 81% and 82%. However, one patient in Group A and 4 in Group B were treated with amiodarone. Assuming this treatment was continued would result in a complete success rate

(no afib, no antiarrhythmics) of 76% in Group A and 64% in Group B.

The researchers also compared the outcome in patients where the PVI was performed without relevant changes due to the location of the esophagus and in those in which the ablation strategy was adjusted due to the proximity of the esophagus to the pulmonary veins. The freedom from afib (with or without antiarrhythmics) in the two

groups after 6 months was 85% and 75% respectively. The researchers conclude that avoiding lesion creation in the vicinity of the esophagus does not have a significant effect on afib recurrence rate during short-term and mid-term follow-up.

Kettering, K, et al. Segmental pulmonary vein ablation: success rates with and without exclusion of areas adjacent to the esophagus. PACE, Vol. 31, June 2008, pp. 652-59

Vitamin C and warfarin

NEWCASTLE, UNITED KINGDOM. The evidence regarding a possible interaction between warfarin (Coumadin) and vitamin C is conflicting. A reduction in INR (shortening of bleeding time) was noted in 2 separate cases involving patients supplementing with 2 grams/day of vitamin C and an unspecified amount respectively. In contrast, a trial in which 5 patients supplemented with 1 gram/day for 14 days revealed no effect of vitamin C on INR. Another trial involving patients given 1 gram/day of vitamin C for 6 months demonstrated no change in required warfarin dosage compared with control patients not supplementing with vitamin C.

Finally, a trial involving 19 warfarin-treated patients given 3, 5, or 10 grams of vitamin C for 7 days showed no clinically important changes in INR, but did result in a 17.5% drop in total plasma warfarin concentration. The researchers involved in this study attribute the decreased absorption of warfarin to the loose stools or diarrhea often accompanying high vitamin C intakes.

A group of researchers at the University of Newcastle now report that normal dietary intakes of vitamin C (20-600 mg/day; 92 mg/day average) has no effect on warfarin clearance from the blood and thus is unlikely to affect INR. Their study involved 57 patients (31 males) who were receiving warfarin. *Wynne, H, et al. Dietary related plasma vitamin C concentration has no effect on anticoagulation response to warfarin. Thrombosis Research, Vol. 118, 2006, pp. 501-04*

Editor's comment: The evidence regarding a possible effect of vitamin C on warfarin clearance and INR is clearly mixed. It would seem though that, while relatively small doses would be expected to have no effect, large doses (3-10 grams/day) may decrease plasma concentrations of warfarin and thus could potentially lead to a drop in INR. From the sparse data available, it would appear that the drop would be relatively minor (from 2.5 to 2.1, for example) and could safely be compensated for by a slight increase in warfarin dosage. In my opinion continuing supplementation (on a steady basis) with 3 x 500 mg/day of vitamin C when on warfarin would be far more beneficial than detrimental.

Warfarin replacements on the horizon

MAGDEBURG, GERMANY. Although there is no evidence that otherwise healthy lone afibbers have an increased risk of ischemic stroke, it is clear that atrial fibrillation (AF) patients with heart failure, diabetes or hypertension have a significantly increased risk and this risk is further magnified if the patient has already suffered a heart attack or stroke. To date, oral anticoagulation with vitamin K antagonists such as warfarin (Coumadin) is still considered to be the best preventive therapy for patients at risk for stroke. Unfortunately, warfarin

interacts with many foods and drugs and treatment requires constant, costly monitoring and substantially increases the risk of hemorrhagic stroke and major internal bleeding, particularly in older people, a group that, ironically, is also most at risk for an ischemic stroke. It is therefore not surprising that a vast amount of medical research is being directed at finding a replacement for warfarin.

Warfarin acts by inhibiting the activation of the vitamin K-dependent coagulation factors V, VII, and

X in the extrinsic and common pathways of the coagulation cascade. Research aimed at replacing warfarin essentially focuses on developing new pharmaceutical drugs which will inhibit specific coagulation factors. Among the more promising agents are:

- **Direct thrombin inhibitors** – The first of these, ximelagatran, showed great promise as a one-size-fits-all, once-a-day effective anticoagulant. Unfortunately, it was found to be toxic to the liver and is now only approved (in Europe) for short-term use such as after knee replacement surgery. A newer direct thrombin inhibitor dabigatran etexilate (Pradax) has successfully undergone 3 large-scale phase III trials for the treatment of deep vein thrombosis (DVT). A recent trial involving 502 AF patients with at least one additional risk factor for stroke found that 150 mg of dabigatran twice a day is as effective and safe as standard warfarin therapy. A very large phase II trial has just finished enrolment of 18,000 AF patients. In this study 2 doses of dabigatran (110 and 150 mg twice a day) will be compared to warfarin therapy. Results are expected by 2009. It is noteworthy that no studies, so far, have observed any excess liver toxicity associated with dabigatran.
- **Direct inhibitors of activated factor X** – two drugs, rivaroxaban and apixaban, are currently being investigated for stroke prevention in AF patients in 2 very large clinical trials involving 14,000 and 15,000 patients respectively. Rivaroxaban would appear to be the most promising of the two. Trials in over 1,000 patients with DVT found that 10-30 mg twice a day and 40 mg once a day were equally effective and had a low rate of bleeding

and adverse events, and no sign of liver toxicity. However, lower doses may be required for patients with renal (kidney) impairment. Other activated factor X inhibitors include otamixaban and betrixaban and an extract from the nematode hookworm (NAP5), which is actually the most potent inhibitor identified so far.

- **Inhibitors of endocardial remodeling** – there is some indication that inhibitors of endocardial remodeling (fibrosis) may be useful in stroke prevention either alone or in combination with one of the above-mentioned drugs. Foremost in the research in this area are the angiotensin II type I receptor blockers (ARBs) which have been found to help block atrial thrombus formation.

The researchers conclude that, “novel anticoagulants or hybrid therapy with a combination of anticoagulants with inhibitors of endocardial remodeling like angiotensin II receptor blockers appear to be attractive future perspective approaches”.

Hammwöhner, M and Goette, A. Will warfarin soon be passé? New approaches to stroke prevention in atrial fibrillation. Journal of Cardiovascular Pharmacology, Vol. 52, July 2008, pp. 18-27

Editor’s comment: It is indeed encouraging to see that a substantial research effort is being directed at replacing warfarin which, in my opinion, is very far from being an ideal stroke prevention remedy. I would not be surprised if a combination of dabigatran and an ARB such as losartan or irbesartan would turn out to be a winner with perhaps rivaroxaban being the “dark horse”. It is very unfortunate that equal effort is not being put into carrying out phase III trials with such natural stroke prevention agents as magnesium, potassium, fish oils, nattokinase, vitamin C, vitamin E, niacin, and vitamin B6.

Gender differences in arrhythmia

TAMPA, FLORIDA. Surveys of lone afibbers generally find that the ratio of men to women is about 80:20. It is by no means clear why this is indeed the case, but the proportion of afib induced

by sustained, vigorous endurance exercise would likely be higher among men. If all cases of atrial fibrillation (AF) are considered, including those involving heart disease, men have a 50% higher risk

of developing AF than do women. The overall prevalence of AF is, however, higher among women because they tend to outlive men.

Other significant differences between men and women when it comes to arrhythmias and the heart in general were summarized in a recent study carried out by cardiologists at the University of South Florida. Among the highlights are:

- The average resting heart rate in women is about 3-5 bpm faster than in men. This may be due to an intrinsic difference in the sinus node.
- Women have longer QT (corrected) intervals than men. NOTE: The QT interval is the duration of the activation (contraction) and recovery of the ventricular myocardium. A prolonged QT interval is associated with ventricular arrhythmias.
- Women are more likely to suffer from supraventricular tachycardia (SVT). Research has shown that SVT episodes are more common during the luteal phase of the menstrual cycle when progesterone levels are elevated.

Inappropriate sinus tachycardia (inappropriately high heart rate at rest [over 100 bpm] and during stress) is also more common among women and is thought to involve abnormal autonomic regulation of the sinus node. Editor's comment: Inappropriate sinus tachycardia is also fairly common after an ablation, perhaps indicating that an ablation can result in a temporary, abnormal regulation of the sinus node.

- Women with AF are more likely than men to suffer an embolic stroke; however, they are also more likely to

experience a major bleeding event if taking warfarin, so stroke prevention in women is particularly challenging. Women with paroxysmal AF tend to have longer episodes and a higher average heart rate during an episode.

- Pulmonary vein isolation (ablation) procedures are equally effective in men and women.
- Women are more likely to experience Torsades de Pointes (a distinctive form of ventricular tachycardia associated with a prolonged QT interval). This means that class 1C antiarrhythmics (flecainide and propafenone) are the preferred antiarrhythmics for women since they do not increase the QT interval. Amiodarone, sotalol, dofetilide and disopyramide may, on the other hand, increase the QT interval and should be used with caution in women.
- In the United States sudden cardiac death (SCD) claims between 300,000 and 400,000 victims every year. The incidence among women is only half of that among men and occurs 10-20 years later in life.
- The risk of SVT increases during pregnancy and during the post-partum period.

The Florida researchers conclude that there are important differences in the presentation and clinical course "of many cardiovascular disorders in men and women. It is important for health care providers to be aware of these differences to provide optimal care for their patients".

Yarnoz, MJ and Curtis, AB. More reasons why men and women are not the same (gender differences in electrophysiology and arrhythmias). American Journal of Cardiology, Vol. 101, 2008, pp. 1291-96

Lifestyle, stress and AF

BOLOGNA, ITALY. In our first LAF Survey (February 2001) one of the questions related to the circumstances preceding the very first episode of afib. The most common trigger for the first one was emotional or work-related stress (26%) followed by

physical overexertion at 24%. Caffeine, alcohol, and ice-cold drinks were next at 10%, 6%, and 8% respectively. A later survey dealt with the triggers of subsequent episodes. Here again, stress and anxiety were high on the list with 94% of adrenergic,

56% of mixed, and 29% of vagal afibbers listing anxiety and emotional and work-related stress as important trigger factors. Caffeine was listed as a trigger for 23% with 31% of adrenergic afibbers experiencing this trigger factor. It is known that both stress and caffeine lead to an increase in sympathetic dominance, so it is not surprising that adrenergic afibbers are particularly vulnerable to stress and caffeine.

A group of Italian researchers now confirm that stressful periods are indeed powerful initiators of a first atrial fibrillation (AF) episode. Their study involved 400 patients (51% men) who presented with a first episode of AF. Their average age was 54 years, and none of them had underlying heart disease. After admission and cardioversion (as needed), the patients were asked how many cups of coffee (espresso) they drank per day and also questioned as to their alcohol and chocolate consumption, smoking habits, physical activity level, and their body mass index (BMI) and waist-to-hip ratio was measured. Finally, all patients underwent a series of cognitive tests to evaluate acute psychological stress during the past 7-30 days. A control group matched for age and gender was selected and evaluated as above.

The researchers found that AF patients had a significantly higher mean life acute stress score (64 LCU) during the week preceding the first episode when compared to the control group (34 LCU). As a matter of fact, the group with a LCU between 75 and 100 had twice the risk of developing afib than did the group with an LCU between 0 and 25. Coffee was another potent trigger with participants drinking more than 3 cups of espresso a day being 3 times more likely to develop afib than were those drinking just 2 cups a day. Obesity (BMI greater than 30) was associated with a relative 61% increase in the risk of experiencing a first afib episode. The researchers found no significant correlations between afib risk and alcohol and chocolate consumption, cigarette smoking, and level of physical activity. They also made the following interesting observations:

- Forty-seven percent of the patients converted spontaneously to normal sinus rhythm within the first 48 hours. Patients with a recent acute stressful event showed the highest probability of spontaneous conversion.
- An increase in coffee consumption was noted in the days after the stressful event and this increase was more pronounced among patients who were not habitual coffee drinkers.

The researchers identify high espresso coffee consumption, a recent acute stressful event, and obesity as independent risk factors for the development of acute lone AF. They also suggest that reducing coffee consumption and avoiding obesity may lead to a reduction in the incidence of AF.

Mattioli, AV, et al. Effect of coffee consumption, lifestyle and acute life stress in the development of acute lone atrial fibrillation. Journal of Cardiovascular Medicine, Vol. 9, No. 8, 2008, pp. 794-98

Editor's comment: The finding that emotional and work-related stress is a trigger factor for afib episodes is not surprising. Nor is it surprising that caffeine was fingered as a culprit. Caffeine consumption results in the release of norepinephrine, the nervous system transmitter that increases sympathetic (adrenergic) activity. Thus adrenergic and mixed afibbers would be vulnerable to over-consumption of caffeine, while it would be expected to affect vagal afibbers much less or not at all. Recent discussions on the Bulletin Board have produced the suggestion that the AF-promoting effects of coffee may be due to the pesticides it contains rather than to the caffeine as such. It is possible that this may be largely true for vagal afibbers, but I don't believe the caffeine effect can be dismissed as far as adrenergic and mixed afibbers are concerned. Nevertheless, drinking organically-grown coffee would certainly be a prudent measure for all afibbers who regularly indulge.

Elimination/Reduction Protocol

Case No. 885

Male afibber – **47 years** of age with **mixed AF** of **12 years standing**; no underlying heart disease

No. of episodes in 6 months prior to starting protocol: **45**

Afib burden in 6 months prior to starting protocol: **630 hrs**

No. of episodes in most recent 6 months after starting protocol: **3**

Afib burden in most recent 6 months after starting protocol: **30 hrs**

Time on protocol: **28 months**

Still need to avoid triggers?: **Yes**

Main components of effective protocol

Trigger avoidance: **MSG, high glycemic index foods, heavy evening meals, stress, physical overexertion, alcohol, mercury (tuna)**

Diet changes: **Zone diet and 4-5 small meals throughout day**

Supplementation: **Magnesium, potassium, taurine, fish oil, coenzyme Q10**

Drug therapy: **Beta-blocker + flecainide**

Stress management: **Regular exercise**

Approaches to shorten episodes: **On-demand beta-blocker + flecainide**

Approaches to reduce ectopics: **Beta-blocker**

Background and details of protocol

I started off with the recommendations in your website and publications. Largely a change in lifestyle with emphasis on taking things a bit easier, avoiding large meals (especially at bedtime) and taking the above supplements, including large doses of fish oil (3 500-mg enteric-coated fish oil capsules and one large fish oil gel cap daily). I also had some benefits from eliminating all tuna (mercury issue) and limiting swordfish to about once/month. Anecdotally, I believe this helped. Also, I believe MSG was a trigger and tried to avoid this. Later, I discovered that a diet with lots of protein and complex carbs (similar to zone diet) was helpful.

Typically I have a hearty breakfast with eggs and some type of low-fat meat (Canadian bacon or turkey sausage or bacon) and some kind of fresh fruit. Just before (late afternoon) exercise, yogurt mixed with more fruit. After exercise a protein shake mixed with a banana and some nuts. Then I try to have a healthy Zone diet type dinner in the evening (meat about the size of a deck of cards and a vegetable). I try to have no bread whatsoever. I also drink about 3 liters of water daily and steer clear of all refined sugar products.

The above protocol was helpful, but I was still having persistent attacks which inhibited my ability to exercise in the day (adrenergic attack) or would wake me up in the middle of the night (vagal). Generally, once the attack went from persistent arrhythmia to full afib, they would go on all night and convert sometime from late morning to early afternoon. Some attacks lasted almost 24 hours. I worked through a cardiologist, who put me on a few beta-blockers and we finally settled on Toprol - 4 x 25 mg. I experimented with the timing of taking the pills and try to take a pill around 11:00, 2:00, 5:00 and 8:00. This helped with the daytime attacks but still not satisfactory. Also would "bite" one or two metoprolol during daytime attacks and this seemed to help me convert back within a couple of hours. Unfortunately, the night time attacks were no better. Metoprolol would not help with evening attacks, and may have made some worse. Many sleepless nights were spent listening to the "frog in my chest trying to get out".

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I strongly considered ablation, but wanted to give procedure development more time so I opted for flecainide. Flecainide proved to be the final "plank" needed for my program. This worked in two ways. The dosage (3 x 50 mg/day) strongly curtailed the frequency of the attacks. Secondly, if I do get an episode, I have taken up to five additional pills (about three is sufficient most of the time) and will convert in 2-4 hours) - I don't believe I have had a single monster 20-24 hr attack since. Added benefit at this point was "normal sinus rhythm promotes more normal rhythm" - it felt like, over time, the attacks become fewer and fewer, which I think is due to some restoration of "normal" heart circuitry.

So to summarize my (largely successful but not perfect) program (in order of perceived effectiveness/benefit is): - 150 mg flecainide - timed to take most in the evening to address vagal attacks; additional "bite down" flecainide to convert if full afib attack occurs; 100 mg Toprol - timed to keep adrenergic attacks (and PACs) to a minimum; additional "bite down" of 25-50 mg of metoprolol if attacks are adrenergic (daytime); strong magnesium and potassium supplementation; avoidance of heavy meals or heavy drinking to avoid vagal attacks; avoidance of severe mental or emotional stress - over working; avoidance of mercury and MSG; heavy doses of fish oil; sitting up or standing during the onset of a vagal attack (i.e. lots of PACs or persistent arrhythmia); sitting down during onset of adrenergic attack; Zone-type diet; exercise (weight training) and cardio exercise (possible since I started taking flecainide); listening to your own body - sense when you are more susceptible and be proactive. And finally, take responsibility for your own "cure" - our current medical establishment will only do so much.

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