THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation!

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In my 2003 research report "Aldosterone: Villain of the Peace" I suggested that an elevated level of aldosterone could be instrumental in the initiation of an episode of lone atrial fibrillation. A small trial involving myself and a curious nephrologist (kidney specialist) confirmed my speculation. My blood levels of aldosterone and cortisol were 50% and 107% higher on the day before an episode as compared to the day after an episode. Urinary potassium and magnesium losses were up 54% and 29% respectively when comparing values for the day before an episode with values on the day following an episode. This supports the idea of aldosterone involvement, but it should be clearly borne in mind that the molecular structure of cortisol is such that it can "dock" at the same mineralocorticoid receptors as aldosterone and thus create the same effects.

A group of German researchers now confirms that elevated aldosterone levels can lead to AF and interstitial fibrosis in the left atrium. They suggest that clinical trials are warranted to evaluate the effect of mineralocorticoid receptor antagonists (spironolactone and eplerenone) in the primary and secondary prevention of AF. An afibber reported in one of our early surveys that he had eliminated his AF through the use of eplerenone.

Also in this issue we report that vitamin D is effective in the prevention of ischemic stroke, that antioxidant therapy may help prevent AF, that longer duration episodes of AF make ablation failure more likely, and finally, that the results of the CONFIRM trial suggest that focal ablation prior to pulmonary vein isolation may improve the outcome for persistent afibbers.

Last but not least, 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 very much appreciated.

Wishing you good health and lots of NSR,

Hans

Highlights

Fish oil supplementation and AF

BROOKLYN, NEW YORK. Fish oils and its main components eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have electrophysiological and anti-inflammatory effects which would be expected to be beneficial in the primary (initial episode) and secondary (recurrence) prevention of atrial fibrillation (AF). For example, fish oils inhibit the sodium and calcium currents in myocytes (heart cells) and enhance potassium currents. They also increase membrane fluidity, decrease inflammation and oxidative stress, and increase effective refractory periods (ERPs), thus decreasing the time interval during which the heart is vulnerable to initiation of an AF episode. Furthermore, fish oil increases vagal activity and improves the function (emptying velocity and fraction) of the left atrial appendage. There is also substantial evidence that fish oil reduces the incidence of fatal

coronary heart disease and sudden cardiac death.

With all these benefits, one would expect fish oils to be effective in preventing both the initiation and recurrence of AF. Unfortunately, there is no consensus that this is universally the case. Electrophysiologists associated with the SUNY Downstate Medical Center have just published a review detailing what is known about the efficacy of fish oils in the primary and secondary prevention of AF. Highlights of their findings follow.

- Continuous fish oil supplementation decreases the risk of developing new-onset AF in patients without structural heart disease.

- Supplementation with high-dose (more than 6 grams/day) fish oil for more than a month reduces the risk of AF episodes originating in the pulmonary veins and reduces heart rate during episodes of paroxysmal AF.

- Fish oil supplementation is beneficial in the primary prevention of AF in the elderly with structural heart disease, but may be detrimental in younger patients with vagal AF. NOTE: Fish oil increases vagal tone.

- There is some evidence from animal studies that fish oil, especially EPA, decreases fibrosis resulting from inflammation.

- No clear evidence exists that fish oil supplementation decreases the risk of recurrence in paroxysmal AF. However, there is evidence that supplementation decreases the risk of early recurrence in patients having undergone a pulmonary vein isolation procedure. This is no doubt related to the anti-inflammatory properties of fish oils. Several clinical trials are underway to finally settle the question – *Is fish oil useful in preventing AF recurrence in paroxysmal and persistent AF*?

- Several clinical trials have been carried out to determine if fish oil supplementation prior to and following coronary artery bypass surgery prevents post-operative AF. Some trials show a benefit, while others do not; however, it is clear that supplementation is associated with a shorter hospital stay, shorter stay in the intensive care unit, and a reduction of post-operative complications.

The authors conclude that there is currently no consensus as to whether fish oil is universally effective in primary and secondary prevention of AF, although there is evidence of benefit for certain subgroups of AF patients.

Kumar, S, et al. Effect of omega-3 polyunsaturated fatty acid supplementation in patients with atrial fibrillation. **Journal of Atrial Fibrillation***, Vol. 5, Issue 2, August 2012, pp. 1-11*

Editor's comment: A survey (LAFS-14) of 190 afibbers revealed that 71% of respondents had tried fish oil supplementation and 18% had found it beneficial (associated with a 50% or more reduction in episode frequency). Thus our survey confirms that fish oil supplementation is not universally beneficial for afib prevention, but may be so for select individuals. Fish oil supplementation, of course, has numerous other benefits independent of any effect on AF, most notably, in the prevention of ischemic stroke, heart attack, and sudden cardiac death.

Support for aldosterone hypothesis

HOMBURG/SAAR, GERMANY. In my 2003 research report "*Aldosterone: Villain of the Peace*" I suggested that an elevated level of aldosterone could be instrumental in the initiation of an episode of lone atrial fibrillation[1]. A small trial involving myself and a curious nephrologist (kidney specialist) confirmed my speculation. My blood levels of aldosterone and cortisol were 50% and 107% higher on the day before an episode as compared to the day after an episode. Urinary potassium and magnesium losses were up 54% and 29% respectively when comparing values for the day before an episode with values on the day following an episode[2]. This supports the idea of

aldosterone involvement, but it should be clearly borne in mind that the molecular structure of cortisol is such that it can "dock" at the same mineralocorticoid receptors as aldosterone and thus create the same effects.

Aldosterone production is usually initiated by activation of the renin-angiotensin-aldosterone system (RAAS) in response to a drop in blood pressure. However, it can also be initiated by ACTH, the same hormone that stimulates the secretion of the stress hormone cortisol. A high potassium level or a low sodium level also causes aldosterone secretion to be increased. A magnesium deficiency causes an increase in aldosterone production and subsequent hypokalemia (potassium deficiency). An excess of calcium ions (Ca++) can also increase aldosterone production because excess Ca++ increases the secretion of ACTH.

A group of German researchers now confirms that elevated aldosterone levels can facilitate atrial fibrillation (AF). Their experiment involved 43 Sprague-Dawley rats that were continuously infused with aldosterone for 8 weeks and 40 controls. At the end of the 8-week period aldosterone level was more than 4 times higher in the "aldo" rats than in controls and potassium level was reduced by 36%. An attempt was made to induce AF by transesophageal atrial burst stimulation. AF was induced in 11 of 11 (100%) aldo rats as compared to 2 out of 9 (22%) in the control group. There was a significant prolongation of p-wave duration in aldo rats (25.6 vs 20.1 ms) and the degree of interstitial fibrosis observed in the left atrium of aldo rats was more than double that observed in controls.

The researchers conclude that aldosterone creates an "AF friendly" substrate characterized by conduction disturbances, atrial fibrosis and myocyte hypertrophy without inducing hypertension. They also observed that aldosterone impeded the function of matrix metalloproteinase-13, the main enzyme responsible for fibrosis reversal in rats. They suggest that clinical trials are warranted to evaluate the effect of mineralocorticoid receptor antagonists (spironolactone and eplerenone) in the primary and secondary prevention of atrial fibrillation.

Reil, JC, et al. Aldosterone promotes atrial fibrillation. **European Heart Journal**, *Vol. 33, 2012, pp. 2098-2108*

Editor's comment: The confirmation that elevated aldosterone levels and by implication, elevated cortisol levels, can create an afib-friendly environment is indeed of great interest as is the confirmation of the ability of aldosterone to create fibrosis in the atria. It should be kept in mind that aldosterone secretion can be initiated by ACTH, an important component in the hormonal cascade activated as a result of chronic stress. It is also worth noting that that many of the triggers implicated in setting off an episode impacts the autonomic nervous system which in turn may set off the stress reaction.

According to several LAF surveys stress (emotional or physical) is the single-most common trigger for afib episodes. It is particularly significant for adrenergic and mixed afibbers with over 90% of adrenergic and 56% of mixed afibbers listing emotional or work-related stress as an important trigger.

Stress is the body's response to an event that upsets its normal balance (homeostasis). Stressors can be physical, emotional, chemical or biological. Examples of physical stressors are vigorous exercise, trauma, exposure to cold, and surgery. The most common chemical stressor, apart from adverse drug and food reactions, is hypoglycemia (low blood sugar). Emotional stressors run the gamut from anxiety to depression, fear of flying, an exam or other difficult mental task, fear of demotion or loss of job, marriage break-up, loss of a loved one, moving house, etc. In short, it can be anything that taxes you emotionally or gives you a gut feeling that something is not right. Bacterial and viral infections and fever are the most common biological stressors. Stress can be acute, like when you face a mugger in a dark alley, or chronic, like when you have to deal with an unreasonable boss every day.

There is evidence that spironolactone and eplerenone can reduce fibrosis formation in heart failure patients so it would seem plausible that these drugs (mineralocorticoid receptor antagonists) could do the same in the case of lone atrial fibrillation. As a matter of interest, an afibber reported in one of our early surveys that he had eliminated his afib through the use of eplerenone.

[1] *Aldosterone: Villain of the Peace*
www.afibbers.org/resources/aldosterone.pdf
[2] Results of aldosterone test
www.afibbers.org/results.pdf

Vitamin D protects against stroke

BOSTON, MASSACHUSETTS. There is convincing evidence that vitamin D, a hormone primarily involved in regulating calcium metabolism, reduces the risk of hypertension and diabetes. Since both of these conditions increase the risk of stroke, it is tempting to speculate that an adequate vitamin D status may also reduce the risk of stroke. A group of researchers from Harvard School of Public Health now confirms that low vitamin D levels are indeed associated with an increased risk of stroke, more specifically, ischemic stroke (stroke associated with a blood clot). Their study had two components:

- Correlating blood plasma level of 25-hydroxyvitamin D (25[OH]D) with incidence of ischemic stroke in a group of 33,000 female nurses taking part in the Nurses' Health Study started in 1976.

- Performing a meta-analysis of 6 studies evaluating the association between 25(OH)D levels and the risk of stroke.

Nurses' Health Study

The researchers prospectively identified and confirmed 464 cases of ischemic stroke. These cases were matched with 464 stroke-free controls of similar age, menopausal status, hormone replacement therapy status, race, and smoking status. After adjusting for a large number of nutritional, disease-related and lifestyle factors, the researchers concluded that women with an average plasma level of 25(OH)D of 35 nmol/L (range of 9.2 to 45.7) had a significantly increased risk of suffering an ischemic stroke (relative risk of 1.53) when compared to those with an average 25(OH)D level of 77.6 nmol/L (range of 65.5 to 264.3). More specifically, a woman with a 25(OH)D level of 55 nmol/L had twice the risk of suffering an ischemic stroke than did a woman with a 25(OH)D level of 95 nmol/L. They also noted that more than 40% of the study participants were deficient in vitamin D as defined as a plasma level of 25(OH)D below 50 nmol/L.

Meta-analysis

Analysis of 6 studies involving 1214 stroke cases found a relative risk of 1.52 when comparing men and women with low vitamin D status with those with high levels of 25(OH)D. One study only considered ischemic stroke and when its results were combined with the results of the Nurses' Health Study, the relative risk of suffering an ischemic stroke associated with a low vitamin D level was 1.59.

Sun, Q, et al. 25-hydroxyvitamin D levels and the risk of stroke. **Stroke***, Vol. 43, June 2012, pp. 1470-77*

Editor's comment: This study clearly links a high plasma level of 25(OH)D with a significantly reduced risk of suffering an ischemic stroke. Although the Nurses' Health Study involved women only, there is no reason to suspect that the results would not be applicable to men. It is noteworthy that the two-fold risk reduction observed at a 25(OH)D level of 95 nmol/L compared to a level of 50 nmol/L is comparable to the risk reduction observed with warfarin therapy. Unfortunately, the diet provides relatively little vitamin D. In the Nurses' Health Study the average vitamin D intake was 350 IU/day resulting in an average 25(OH)D level of 56 nmol/L. To reach a level of 95 nmol/L would require supplementation with about 4000 IU/day.

Focal ablation for atrial fibrillation (CONFIRM trial)

SAN DIEGO, CALIFORNIA. Since 1998 when Prof. Haissaguerre and colleagues in Bordeaux discovered that 94% of AF episodes are triggered by impulses originating in the pulmonary veins, the mainstay of catheter ablation for atrial fibrillation (AF) has been pulmonary vein isolation (PVI) in which the pulmonary veins are electrically isolated from the left atrium by rings of lesions created by cauterizing the heart tissue with catheters powered by radiofrequency energy or liquid nitrogen (cryoablation). There are two mapping approaches used to guide the ablation catheter.

- **Segmental PVI (Haissaguerre/Natale protocol)** in which electrophysiological mapping (using a multipolar Lasso catheter) is used to locate the pathways taken by aberrant impulses from the pulmonary veins. Once found, the pathways are eliminated by ablation around the veins

approximately 5 to 10 mm from the ostium of the veins.

- **Circumferential anatomical PVI (Pappone protocol)** in which the anatomy, rather than the electrophysiological properties of the junction between the pulmonary veins and the left atrium are mapped, usually using a CARTO or Nav-X system. The anatomical structure shown on a computer screen is used to guide the creation of two lesions rings in the left atrium – one completely encircling the left pulmonary veins and another completely encircling the right pulmonary veins; the two rings are usually joined by a linear lesion.

The two protocols are about equally effective when it comes to paroxysmal AF; however, in the case of persistent and permanent AF, the Haissaguerre/Natale protocol is superior because the "trouble spots" or focal points involved in persistent/permanent AF, as well as in paroxysmal AF with long episodes (24 hours or greater) are located, not within the lesion rings encircling the pulmonary veins, but rather on the walls of the left and right atria, or in specific structures of the heart such as the left atrial appendage or the *crista terminalis* or superior vena cava in the right atrium. An electrophysiologist (EP) skilled in interpreting the information received during an electrophysiological study is far more likely to find and successfully ablate these trouble spots than an EP who relies solely on anatomical mapping.

The existence of focal points (reentrant circuits) in the atria liable to initiate AF has probably been known for a hundred years and ablation based on eliminating them was the norm prior to 1998, but with rather limited success. We now appear to have come full circle with the rediscovery of the importance of targeting these focal points or rather areas (local electrical rotors and focal impulse sources) in ablations, especially in the case of persistent AF.

Dr. Sanjiv Narayan and colleagues at the University of California at San Diego now report the results of the CONFIRM trial involving the mapping and elimination of focal impulse and rotor modulation (FIRM) with the aid of a 64-pole basket catheter and a sophisticated computer program known as the Topera system. The clinical trial involved 92 patients who underwent a total of 107 procedures (31 for paroxysmal AF and 76 for persistent AF). Thirty-six (34%) of the procedures were performed using FIRM-guided ablation followed by an anatomically-guided PVI. The FIRM-guided procedures included mapping and appropriate ablation in the right atrium as well.

The remaining 71 procedures were conventional anatomically-guided PVIs with an added left atrial roof line, again based on anatomic guidance. It would appear that no electrophysiological mapping was used during these procedures, nor was the right atrium mapped, or any effort made to locate and eliminate focal sources which can only be found using electrophysiological mapping. This would seem to be an unfortunate omission for the patients with persistent AF (66% of procedures were for persistent AF).

Not surprisingly, the outcome of the FIRM-guided procedures was far superior to the outcome of the conventional procedures. Patients were evaluated at 3, 6, 9, 12, 18 and 24 months and the incidence of AF episodes (recorded on implanted ECG monitors/ICDs, or with 7-day patient activated event recorders) was noted. An average (median) 273 days after their procedure, 82.4% of the participants of the FIRM-guided ablation group were AF-free as compared to only 44.9% in the conventional ablation group. The UCLA researchers conclude that the results of the FIRM-guided approach offer "*a novel mechanistic framework and treatment paradigm for AF*."

Narayan, SM, et al. Treatment of atrial fibrillation by the ablation of localized sources. **Journal of the American College of Cardiology***, Vol. 60, August 14, 2012, pp. 628-36*

Kuck, K-H and Wissner, E. A FIRM grip on atrial fibrillation. **Journal of the American College of Cardiology***, Vol. 60, August 14, 2012, pp. 637-38*

Editor's comment: Despite the clearly biased design of this trial, it certainly is encouraging to see a 2-year success rate of 82% for persistent afibbers. However, it should be kept in mind that the FIRM-guided approach was only used in 36 procedures. Independent confirmation of the efficacy of the approach obviously needs to be obtained before it can be declared "the future of ablation". Nevertheless, if efficacy is indeed confirmed, the approach will be of significant benefit, especially for EPs who are now relying on anatomical rather than electrophysiological mapping to guide their ablation procedures. NOTE: I find it difficult to reconcile the statements "single-procedure success rate" and "repeat ablation was not permitted" with the fact that the trial involved 92 patients who underwent a total of 107 procedures.

Antioxidant therapy for AF

CHICAGO, ILLINOIS. In my first book *Lone Atrial Fibrillation: Towards A Cure*, I suggested that oxidative stress, caused by an imbalance between reactive oxygen species (ROS) and the body's natural antioxidant defences, could be a precipitating factor for atrial fibrillation (AF) episodes. The majority of paroxysmal episodes originate in the pulmonary veins, which are constantly exposed to highly oxygenated blood flowing through relatively narrow veins, and thus creating substantial shear stress. The combination of a high oxygen pressure and shear stress is a potent breeding ground for 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.

The oxidative stress would be magnified in endurance athletes who also happen to have a 5 times higher incidence of lone AF as compared to the general population. 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. Researchers at the Cleveland Clinic and Ohio State University have found that AF patients show signs of extensive oxidative injury to their myofibrillar creatine kinase (MM-CK). MM-CK is involved in the control of the contraction of individual heart cells (myocytes). The researchers also determined that the oxidative damage was caused by peroxynitrite, a highly potent free radical. They conclude that peroxynitrite-induced oxidative stress can damage individual heart cells to such an extent that their normal function is disrupted and atrial fibrillation results[1].

The Cleveland Clinic researchers later followed up these initial findings by an experiment designed to show whether reducing the level of peroxynitrite through the use of an antioxidant (vitamin C) would prevent surgery-induced atrial fibrillation. Their clinical trial involved 50 bypass surgery patients who were given 2 grams of ascorbic acid (extended release) the night before surgery, followed by 500 mg doses twice daily for 5 days after surgery. The incidence of postoperative AF in the vitamin C group was 16.3% as compared to 34.9% in a comparable group not given vitamin C. The researchers conclude that AF episodes are sustained by oxidative stress and increased peroxynitrite generation caused by the rapid heart rate[2].

Drs. Sovari and Dudley at the University of Illinois at Chicago now provide further evidence supporting the idea that oxidative stress may be a significant cause of AF. They found that the concentration of ROS derivatives and the ratios of oxidized to reduced glutathione and cysteine are increased in the blood of patients with AF. Other researchers have reported that oxidative stress is associated with abnormal intracellular handling of calcium ions and a decrease in connexin43. There is also evidence that ROS can increase cardiac fibrosis.

The University of Illinois researchers claim that strengthening antioxidant defences using currently available antioxidants is unlikely to be successful in eliminating AF and suggest that a more fruitful approach may be to develop drugs that target the sources of ROS. Among the more important of these are mitochondria, the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and uncoupled nitric oxide synthase (NOS). NADPH oxidase produces large amounts of superoxide radicals and its activity has been shown to be increased in AF patients. The authors conclude that developing drugs targeting NADPH oxidase and/or drugs that will activate natural antioxidant defense mechanisms of individual heart cells (myocytes) may be an effective approach to preventing AF.

Sovari, AA and Dudley, SC. Antioxidant therapy for atrial fibrillation: lost in translation? **Heart**, *August 15, 2012 [Epub ahead of print]*

Editor's comment: It is known that vitamin C helps to regenerate the body's natural antioxidant, glutathione peroxidase, which also requires selenium for its synthesis. Gamma-tocopherol is highly effective in trapping reactive nitrogen dioxide specimens, while lycopene is very effective in neutralizing (quenching) a highly reactive form of oxygen called singlet oxygen. Finally, ubiquinol (ubiquinone or coenzyme Q10) is another very effective antioxidant which specifically targets ROS originating in mitochondria. Thus, there would

seem to be no lack of natural antioxidants which, in the optimum form and combination, might help prevent AF. Several of them have been evaluated for preventing post-operative AF and vitamins C and E have been found to be effective as has N-acetylcysteine. I am not aware of any clinical trials aimed at evaluating the effect of natural antioxidants on the prevention of lone AF.

[1] Mihm, Michael J., et al. Impaired myofibrillar energetics and oxidative injury during human atrial fibrillation. Circulation, Vol. 104, July 10, 2001, pp. 174-80

[2] Carnes, Cynthia A., et al. Ascorbate attenuates atrial pacing-induced peroxynitrite formation and electrical remodelling and decreases the incidence of postoperative atrial fibrillation. Circulation Research, Vol. 89, September 14, 2001, pp. e32-e38

Longer episodes associated with ablation failure

NIEUWEGEIN, THE NETHERLANDS. It is well established that achieving a successful outcome of catheter ablation procedures for persistent and permanent atrial fibrillation (AF) is significantly more difficult than in the case of paroxysmal (intermittent) AF. There is also substantial evidence that a left atrial parasternal diameter greater than 55 mm (5.5 cm) is associated with a poorer outcome. Now a group of Dutch electrophysiologists reports that pre-procedure AF burden, more specifically the longest episode duration, is a strong predictor of outcome.

Their study involved 120 patients with symptomatic paroxysmal AF, but no significant structural heart disease (lone AF). All patients underwent a pulmonary vein isolation (PVI) procedure with a ring-shaped, multielectrode ablation catheter using alternating unipolar- and bipolar-phased radiofrequency energy. Patients were kept on antiarrhythmics during a 3-month blanking period and were then followed up at 6, 12, 18, and 24 months following the procedure. Follow-up included standard ECGs, 2-day and 7-day Holter monitoring at follow-up appointments and when patients reported symptomatic AF.

At the one-year follow-up, 66 patients (55%) were off antiarrhythmics and free of any atrial arrhythmia (AF, atrial flutter and tachycardia) after a single procedure, while another 10 (8%) were arrhythmia-free with the aid of amiodarone or Class I antiarrhythmics (propafenone, flecainide). At the 2-year follow-up, 49% were free of arrhythmia without the aid of drugs after a single procedure.

The researchers observed that longer duration of AF (years), longer duration of episodes (mean), and longer duration of the longest episode were all associated with poorer outcome. The average number of episodes per month in the group was 19 and, oddly enough, more frequent episodes prior to the procedure were associated with a greater chance of success. However, after multivariable analysis, the only pre-procedural variable predicting outcome was the duration of the longest episode.

In the successful group, the average duration of the longest episode was 33 hours as compared to 48 hours in the unsuccessful group. The only procedural variable predicting outcome was the need for electrical cardioversion during the procedure. Only 10% of the members of the successful group required cardioversion as compared to 36% in the unsuccessful group.

Mulder, AAW, et al. Freedom from paroxysmal atrial fibrillation after successful pulmonary vein isolation with pulmonary vein ablation catheter-phased radiofrequency energy. **Europace***, Vol. 14, 2012, pp. 818-25*

Editor's comment: The findings of this study confirm that a single PVI without additional lesions is not adequate to deal with AF involving long-duration episodes. This, in reality, means that a circumferential, anatomically-guided PVI is less likely to be successful than a segmental, electrophysiologically-guided procedure (Haissaguerre/Natale protocol) when it comes to dealing with cases involving long-duration episodes. It also means that afibbers who are contemplating having a catheter ablation procedure should do so before their episodes become day-long. In my own case, when asked by Prof. Pierre Jais in Bordeaux whether I ever had experienced episodes lasting longer than 24 hours, my answer was yes. He remarked that in this case a standard PVI would not do the job, and that he would have to go "hunting" for offending foci on the left atrial wall and other "usual suspects".

Long-term outcome following ischemic stroke

ATHENS, GREECE. There is still no consensus as to whether type of atrial fibrillation (paroxysmal, persistent or permanent) affect the risk of suffering an ischemic stroke, although the preponderance of evidence points to the risk being similar for all three types, with permanent AF perhaps having a slightly higher risk. A group of Greek physicians at the Alexandra Hospital in Athens now reports on a study aimed at determining the association between AF type and the long-term outcome (recurrence rate and mortality) in patients with non-valvular AF who had suffered an ischemic stroke.

The study involved 811 patients (52% women) of which 34.2% had paroxysmal AF, 20.3% had persistent, and the remaining 45.5% had permanent AF. Patients with permanent AF were older (mean age of 77 years), 77% had hypertension, 14% had heart failure, and 20% were on warfarin or other vitamin K antagonists when they suffered a first ischemic stroke. In contrast, patients with paroxysmal AF were younger (mean age of 74 years), and were less likely to have hypertension (69%) and heart failure (8%). Patients were followed for an average of about 3 years. Stroke recurrence during the first 30 days was 4.3% for paroxysmal AF vs. 11.9% for permanent AF. Ten-year recurrence rate (estimated from Kaplan-Meyer curves) was 33.5% for paroxysmal AF vs. 41.4% for permanent AF. Similarly, 10-year overall survival rate was more than twice as high amongst paroxysmal afibbers (34.6%) than amongst permanent afibbers (15.8%).

The researchers speculate that the lower rate of stroke recurrence in paroxysmal AF could be explained by the concept that thromboembolic risk in AF depends on the duration of the episode. They also point out that stroke severity and subsequent disability were significantly lower amongst paroxysmal afibbers and suggest that the reason for this is that short, paroxysmal episodes lead to the formation of thrombi of relatively smaller size compared to those formed in permanent AF. They conclude that paroxysmal afibbers have lower rates of recurrence and mortality compared to those with permanent AF.

Ntaios, G, et al. The type of atrial fibrillation is associated with long-term outcome in patients with acute ischemic stroke. **International Journal of Cardiology***, May 16, 2012 [Epub ahead of print]*

Editor's comment: Although the patients involved in this study were by no means lone afibbers (about 20% had coronary artery disease and about 10% had heart failure), it would seem reasonable to assume that lone afibbers with paroxysmal AF who suffer an ischemic stroke have a better long-term prognosis than do those with permanent AF.

Predicting recurrence following catheter ablation

TURIN, ITALY. Electrophysiologists have placed a great deal of emphasis on establishing the factors determining the long-term outcome of catheter ablation for atrial fibrillation (AF). It is generally accepted that achieving a successful outcome is more challenging when it comes to persistent and permanent AF than in the case of paroxysmal AF. Some studies have also found an enlarged left atrium to be detrimental to success, and a recent Dutch study concluded that long-duration paroxysmal episodes prior to the first ablation are associated with a poorer outcome. Now an international group of researchers with participants from Italy, United Kingdom, China, Japan, Taiwan, and the USA reports on a meta-analysis of 19 studies aimed at determining factors affecting mid-term success and procedural complications.

The analysis included 7200 patients and over 9000 procedures. The majority (60%) had paroxysmal AF, 15% had persistent, and 25% had permanent AF. The average age of the patients was 57 years and 77% were male. Fifteen percent of patients had a history of heart disease or heart failure, 44% had hypertension, and the average left atrial diameter was 42 mm. All patients underwent an initial pulmonary vein isolation (PVI) procedure with 27% receiving additional linear lesions and 15% having complex fractionated atrial electrograms ablated as well. After an average follow-up of 22 months and 1.23 procedures per patient, 69% of patients were in normal sinus rhythm corresponding to a recurrence rate of 31%. NOTE: It is not clear whether this number included patients still on antiarrhythmics. The recurrence rate in studies where follow-up exceeded 30 months was 34% or a 66% success rate.

Although the success rate for persistent AF was significantly lower than for paroxysmal AF, after the initial procedure there was no significant difference after redo procedure(s). The authors conclude that the following variables are detrimental to mid-term success:

- Recurrence of AF within 30 days after ablation;
- Valvular atrial fibrillation;
- Left atrial diameter in excess of 50 mm.

In-hospital complication rates associated with the 9000 procedures were low with tamponade requiring drainage occurring in 0.99% of cases, strokes/TIAs with no after-effects occurring in 0.36%, and stroke with persistent impairment occurring in 0.22% of cases.

D'Ascenzo, F, et al. Which are the most reliable predictors of recurrence of atrial fibrillation after transcatheter ablation? **International Journal of Cardiology**, *May 22, 2012 [Epub ahead of print]*

Editor's comment: This study adds to previous data showing that the following variables are important predictors of a negative ablation outcome:

- Longer duration of paroxysmal episodes;
- Recurrence within 30 days of ablation;
- Valvular atrial fibrillation;
- Left atrial diameter in excess of 50 mm;
- Need for cardioversion during procedure;
- An elevated level of C-reactive protein prior to procedure;
- Having experienced no benefit from antiarrhythmic drugs;
- Low left ventricular ejection fraction;
- Enduing AF for too long before having an ablation.

Although recurrence within 30 days of ablation does increase the risk of recurrence, it is by no means an absolute indication of failure.

Frequent PACs may predict AF

HONG KONG, CHINA. PACs, also known as atrial extra systoles or atrial premature beats, are extremely common and can be found on 24-hour Holter monitoring in over 60% of normal adults. They are usually entirely benign and do not require treatment unless they are very frequent or result in uncomfortable palpitations. PACs originate from foci of "rogue" heart cells that decide to take on a beat of their own. Depending on when the PAC "fires", it may not be transmitted to the ventricles at all but, in some cases, it may cause a pause in the normal heart beat rhythm, which may or may not be followed by a more forceful ventricular contraction.

PACs can be precipitated by stress, fatigue, fever, thyrotoxicosis, tobacco, caffeine, and certain other stimulants and drugs including cold medications and weight-loss preparations. PACs may also be a sign of underlying heart disease such as heart failure or myopericarditis. PACs can initiate atrial fibrillation (AF), atrial flutter or supraventricular tachycardia. Research has shown that these arrhythmias originate from the same focal points that generate PACs. PACs can be distinguished fairly easily on an electrocardiogram; they are characterized by a smaller and earlier than expected P wave. The P wave originates in the sino-atrial node and is the electrical impulse that initiates the heart beat.

The obvious way to avoid PACs is to avoid the triggers. In more severe cases minor tranquillizers or beta-blockers may prove helpful. There is also substantial evidence that a magnesium deficiency can increase both PACs and PVCs (premature ventricular complexes), and that magnesium supplementation can reduce them very significantly.

A group of researchers from the University of Hong Kong now reports that frequent PACs may predict the occurrence of new onset AF and may be associated with an increased incidence of stroke, heart failure, and cardiac-related death. Their study involved 428 patients without AF and structural heart disease who underwent 24-hour monitoring for palpitations, dizziness or syncope (temporary loss of consciousness). The average age of the patients was 66 years and 44% were male. The study participants were not entirely healthy with 45% having hypertension, 17% having diabetes, and 17% having coronary artery disease. About 45% were on calcium channel blockers and 44% were on beta-blockers.

More than 100 PACs a day was considered to be frequent and 107 of the 428 patients (25%) fell into this category. Patients with frequent PACs were likely to be older (71 years vs. 65 years) and were more likely to be smokers (36% vs. 25%). After a mean follow-up of 6 years, 29% of the patients in

the frequent PACs group had developed AF as compared to 9% in the non-frequent PACs group. This corresponds to an incidence of 4.83%/year in the frequent PACs group as compared to 1.43%/year in the non-frequent group.

Cox regression analysis revealed that frequent PACs (HR: 3.22), age over 75 years (HR: 2.3), and coronary artery disease at baseline were independent predictors of new onset AF. Cox regression analysis also showed that age over 75 years (HR: 2.2), coronary artery disease (HR: 2.2), and frequent PACs (HR: 1.6) were independent predictors of ischemic stroke, congestive heart failure, and death.

The researchers point out that another study, which involved 687 apparently healthy individuals using 720 or more PACs a day (30 per hour) as the definition of frequent PACs, reported an incidence of new onset AF of 1.28%/year in the frequent PACs group as compared to 0.43% in the non-frequent group.

Chong, BH, et al. Frequent premature atrial complexes predict new occurrence of atrial fibrillation and adverse cardiovascular events. **Europace**, *Vol. 14, 2012, pp. 942-47*

Editor's comment: Although current afibbers clearly do not need to worry about developing AF, it is of interest to note that frequent PACs may be associated with an increased risk of adverse cardiovascular events. Fortunately, PACs and PVCs can pretty well be eliminated by ensuring adequate magnesium and potassium status.

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