It is estimated that 53,000 ablation procedures for atrial fibrillation were performed worldwide in 2006 with 25,000 of those taking place in the United States. Obviously, there is a huge and growing demand for ablation – a demand that, realistically, can only be met by the development of new techniques and equipment, which will enable less experienced EPs to achieve a high rate of success.

In this issue, we report on two such new approaches, the Box isolation approach which Japanese researchers have found to be highly successful in paroxysmal AF, and the remote magnetic navigation system developed by Stereotaxis. Although this system (Niobe II) probably is unsurpassed in its ease of catheter navigation, there are, according to Cleveland Clinic researchers, still serious problems with the efficacy of the ablation tip itself.

Also in this issue we report on dronedarone, an analogue of amiodarone, which shows promise in its first major trials; pre- and post-ablation treatment with statin drugs and ACE inhibitors does not improve ablation outcome, but there is some indication that treatment with angiotensin receptor blockers may; and a combination of vitamin C and vitamin E looks promising for stroke prevention in patients with cardiovascular disease – there is no reason why it should not work equally well for those without heart disease.

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

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Electrocardiogram may predict development of AF

GHENT, BELGIUM. As the heart muscle contracts it generates a current that spreads into the fluids surrounding the heart and can be measured on the surface of the body. An electrocardiogram (ECG) measures the electrical activity of the heart. It involves the placing of small electrodes on the chest around the heart area and on the arms and legs, usually using a total of 12 leads. A normal ECG shows a characteristic form consisting of a P wave, a QRS complex, and a T wave. The start of the P wave is the start of an individual contraction (heart beat) and the beginning of the depolarization of individual myocytes (heart cells). In healthy young men the mean duration of the P wave is about 77 milliseconds (52-115 ms).[1]

Researchers at Ghent University now report that it may be possible to predict the development of atrial fibrillation (AF) as much as 10 years before the first episode actually occurs. Their study included 40 patients aged 55 to 74 years who were participants in the Belgian Interuniversity Research on Nutrition and Health Survey. After a 10-year observation
period, these patients had all developed AF. Their baseline ECGs were compared to those of 120 study participants (matched for age and gender) who had not developed AF.

The researchers noted that the participants who developed AF were more likely to suffer from hypertension and to be overweight, although not obese (BMI < 30). However, the most interesting observation was that participants who developed AF had substantially longer P waves at baseline than did those who did not (mean P wave duration 120 ms vs. 110 ms). It was also apparent that the presence of a deflected P wave (a wave with a slight indent in the down slope) was significantly more common among those destined to develop AF (55% vs. 13%). Overall, the researchers estimate that a patient with a long-duration, deflected P wave has a 13-fold greater risk of developing AF within a 10-year period than do gender and age matched controls with normal P waves. De Bacquer, D, et al. Long-term prognostic value of P-wave characteristics for the development of atrial fibrillation in subjects aged 55 to 74 years at baseline. American Journal of Cardiology, Vol. 100, 2007, pp. 850-54

Editor's comment: The prevalence of heart disease (heart attack, angina, and left ventricular hypertrophy) was less than 10% in the groups studied, so if it is likely that the results of the above study would be applicable to lone AF as well. Thus, the careful study of P wave shape and duration on a routine ECG could perhaps be used to give advance warning of an increased risk for the development of AF and thus motivate people to take preventive measures such as reducing emotional and work-related stress, moderating vigorous physical activities, and go easy on caffeine and alcohol. It is also of interest that P wave duration can be used to predict whether or not paroxysmal AF will turn into permanent (chronic) AF.


A vitamin C + vitamin E combination may help prevent stroke

BOSTON, MASSACHUSETTS. Despite the fact that antioxidants such as vitamin C and vitamin E exert their beneficial effects by delaying the ONSET of certain age-related diseases, the medical community continues to attempt to disprove their benefits by applying them to patient populations who are already sick. This is disingenuous at best, blatantly dishonest at worst. Dietary antioxidants (in commonly used doses) are effective in PRIMARY prevention of disease, NOT in SECONDARY prevention, i.e. for patients already suffering from disease (heart disease, cancer, etc).

Researchers at the Brigham and Women’s Hospital and the Harvard Medical School recently reported yet another clinical study designed to prove the worthlessness of dietary antioxidants. The patient population consisted of 8171 female health professionals above the age of 40 years. The majority (64%) had been diagnosed with cardiovascular disease and the remaining 36% had 3 or more risk factors for cardiovascular disease (hypertension, high cholesterol level, diabetes, or a family history of heart attack). About 77% of the group was overweight with 48% being obese.

The women were randomized to receive placebo, vitamin C (500 mg/day of synthetic ascorbic acid), vitamin E (600 IU every second day of d-alpha-tocopherol acetate), or a combination of vitamins C and E. A subgroup also received 50 mg every other day of synthetic beta-carotene either with or without vitamins C and E. During an average follow-up of 9.4 years, 274 of the women experienced a heart attack (myocardial infarction), 889 underwent angioplasty or bypass surgery, and 395 died from cardiovascular events.

There was no difference in the overall incidence of cardiovascular events among women who had supplemented with vitamin C and those who had been given placebos. However, patients who had been given vitamin E (and had stuck with the regimen) experienced a statistically significant 13% reduction in cardiovascular events over the follow-up period, a 22% reduction in heart attacks, and a 27% reduction in stroke. Overall, the incidence of heart attack, stroke and cardiovascular death was reduced by 23% in the group of vitamin E supplementers who continued their supplementation throughout the trial period. Furthermore, participants who had been randomized to take both
vitamin C and vitamin E experienced a statistically significant 31% reduction in stroke incidence.

The researchers conclude that, "There were no overall effects of ascorbic acid, vitamin E, or beta-carotene on cardiovascular events among women at high risk for CVD". They also conclude that, "We found no detrimental effects of any of these agents on total or CVD mortality". In other words, while antioxidant supplementation may be of no value, it is at least not likely to cause any harm. The researchers also make the following interesting comment:

"For vitamin E, there have been suggestions that gamma tocopherol is a more powerful antioxidant. Supplementation with alpha tocopherol depletes gamma tocopherol, which may explain the lack of effect seen in vitamin E trials".

In other words, they used the least effective form of vitamin E in their trial, one that will, in addition, deplete the level of the most effective form.


Editor’s comment: This is clearly another hatchet job on antioxidants. Only by including participants who had not been following the study protocol (i.e. those who had NOT been taking antioxidants as directed) were the researchers able to "prove" that antioxidants have no benefit in SECONDARY prevention. When those participants who had not followed the protocol were censored out, vitamin E proved to be highly effective, and a combination of vitamin C and E actually reduced stroke incidence by 31% - a performance significantly better than that of aspirin.

Sleep apnea and cardiac arrhythmias

TOLEDO, SPAIN. Obstructive sleep apnea (intermittent loss of breathing during sleep) is a common disorder affecting about 4% of middle-aged American men and about 2% of middle-aged American women. It is strongly linked to increasing age and obesity. Obstructive sleep apnea (OSA) is characterized by a collapse of soft muscle tissue in the throat leading to blockage, restricted airflow and ultimately deoxygenation of red blood cells. OSA can be diagnosed during a sleep study (polysomnography) and its severity is described via the apnea-hypopnea index (AHI), which represents the number of obstructive respiratory events per hour of sleep. An AHI of less than 10 is considered normal, an AHI of 10-20 is mild, 20-30 is moderate, and more than 30 events per hour characterizes severe OSA. OSA can usually be successfully treated by the use of a continuous positive airway pressure (CPAP) machine which supplies a constant, uninterrupted flow of air pressurized just enough to keep the airway open.

OSA is an insidious disorder that, if left untreated, can cause a number of serious problems including increased heart rate, blunted heart rate variability, systemic inflammation, atherosclerosis, arterial hypertension, insulin resistance, type II diabetes, and increased risk of inappropriate blood coagulation.

Cardiac arrhythmias are common in patients with OSA. They occur mainly at night, in contrast with arrhythmias in patients with structural heart disease, which occur mainly during daytime. A nighttime AF episode in an OSA patient starts out with a bradycardia (abnormally low heart rate) due to parasympathetic (vagal) hyperactivity followed by tachycardia (an abnormally high heart rate) as a consequence of awakening from sleep. Nighttime bradycardia and subsequent AF episodes in OSA patients can, in most cases, be avoided by the use of a CPAP machine. A recent study observed OSA in 49% of 151 patients with atrial fibrillation, so it clearly is not an uncommon cause of AF. It is also of interest to note that patients with OSA tend to have a greatly increased frequency of premature ventricular beats (PVCs) during sleep as compared to the frequency during wakefulness. They also, in general, tend to have more ventricular ectopy (non-sustained ventricular tachycardia and ventricular bigeminy, trigeminy, and quadrigeminy). Again, treatment with a CPAP machine has been found to reduce ventricular ectopy quite substantially.

Arias, MA and Sanchez, AM. Obstructive sleep apnea and its relationship to cardiac arrhythmias. Journal of Cardiovascular Electrophysiology, Vol. 18, September 2007, pp. 1006-14

Editor’s comment: It is clear that OSA is a common condition that can lead to many serious disorders. A connection with AFib is also clear and there is growing evidence that the use of a properly calibrated CPAP machine cannot only prevent OSA, but may prevent OSA-related AFib as well. Thus afibbers who have interrupted sleep, daytime
sleepiness, or a greater incidence of PVCs (measured on a Holter monitor) during the night might do well to consider a properly conducted sleep study and the use of a CPAP machine if indicated.

### Maintenance of sinus rhythm post-ablation

MAYWOOD, ILLINOIS. As the number of patients with atrial fibrillation continues to grow, the number of ablation procedures is increasing as well. It is estimated that 53,000 ablation procedures for AF were performed worldwide in 2006 with 25,000 of those taking place in the United States. Although the majority of procedures are initially deemed successful, the recurrence rate can be high primarily depending on the skill of the electrophysiologist (EP) performing the ablation. Post-ablation treatment has been tried with several drugs, particularly anti-inflammatories, but so far none have been successful.

Researchers at the Loyola University Medical Center now report on their evaluation of statin drugs (such as atorvastatin, lovastatin and simvastatin), ACE inhibitors (such as enalapril, lisinopril and ramipril), and angiotensin receptor blockers (ARBs) (such as candesartan, irbesartan, losartan and valsartan) in the pre- and post-ablation treatment of afibbers. Their study involved 132 paroxysmal and 45 persistent afibbers. The majority (71%) were men, 23% had structural heart disease, and 43% had hypertension. Fifty patients (28%) were on statin drugs for at least one month prior to their ablation procedure and remained on these drugs for the average (mean) follow-up period of 13.8 months. Thirty-one patients (18%) were on ACE inhibitors and 18 patients (10%) were on ARBs during the study period (from one month prior to ablation to 13.8 months post-ablation). The study participants all underwent antral pulmonary vein isolation with right flutter ablation where necessary.

At the end of the follow-up period, 75% of paroxysmal afibbers and 63% of persistent afibbers were free of afib for an overall success rate of 72%. However, 13% of those in sinus rhythm were still taking antiarrhythmic drugs, so the performance was actually:

- Full success (no afib, no drugs) 59%
- Partial success (no afib, but on antiarrhythmics) 13%
- Failure 28%

The main indicator of failure was a low left ventricular ejection fraction prior to the procedure.

The researchers observed no benefits of statin drugs on the maintenance of sinus rhythm. In the group not taking statin drugs 74% of patients remained in sinus rhythm, while only 66% in the group taking statins did so. ACE inhibitor treatment showed no advantage either, with only 55% of patients being in sinus rhythm at the end of the follow-up. The small group (18 patients) on ARBs, however, showed an intriguing trend towards better success. At the end of follow-up, 94% of them were still in normal sinus rhythm. Although this is clearly a very small number of patients upon which to base a conclusion, the researchers suggest that larger, prospective, randomized studies would be in order to follow up on these promising findings.

Chekakie, MO, et al. The effects of statins and renin-angiotensin system blockers on atrial fibrillation recurrence following antral pulmonary vein isolation.

Editor’s comment: It is known that the renin-angiotensin system (RS) exhibits pro-inflammatory actions and plays a direct role in the electrical and structural remodeling that takes place in the left atrium during atrial fibrillation. Thus, inhibiting it pre- and post-ablation seems to make sense. Nevertheless, the purpose of a radiofrequency ablation is to create scar tissue (fibrosis) around the pulmonary veins in order to create a barrier to AF propagation. Treatment with drugs that interfere with fibrosis formation may, in fact, affect the integrity of the ablation line and thus promote afib recurrence. This may explain why statins and ACE inhibitors proved ineffective, or perhaps even slightly detrimental, to maintenance of sinus rhythm. ACE inhibitors and ARBs, on the other hand, have
different biological activity, which could explain the superiority of ARBs. The possible benefits of ARBs in post-ablation sinus rhythm maintenance clearly need to be established (or disproved) in larger trials.

Results of dronedarone trial

LOS ANGELES, CALIFORNIA. Although amiodarone (Cordarone, Pacerone) is not approved by the FDA for the treatment of atrial fibrillation, it is nevertheless widely prescribed for this condition. It can be very effective in preventing paroxysmal AF, but has the disadvantage of potential serious adverse effects involving the lungs, kidneys, liver, thyroid, nervous system, and skin. Another disadvantage of amiodarone is its long elimination half-life of 30-55 days. Most of the problems associated with amiodarone are believed to be due to the presence of iodine in the drug. Not surprisingly, this has led to the development of dronedarone, an amiodarone analogue without the iodine component.

Two large clinical trials aimed at evaluating the safety and efficacy of dronedarone have just been completed. One, the EURIDIS trial, involved 612 patients with paroxysmal or persistent AF recruited from 12 European countries. The other, the ADONIS trial, involved 625 afibbers (none with permanent AF) recruited in the USA, Canada, Australia, Argentina, and South Africa. In the combined trials 828 patients were randomized to receive 400 mg twice a day of dronedarone, while the remaining 409 patients received a placebo. All patients were in sinus rhythm at the start of the trial. Patients with congestive heart failure and ventricular dysfunction were excluded from the trial as were those with a resting heart rate below 50 bpm. Trial participants were closely monitored through regular follow-up visits and all were given transtelephonic electrocardiographic monitors for use at regular intervals and when they experienced an afib episode. The main results of the trials were (results combined for the two trials):

- The majority of documented first recurrences were symptomatic (palpitations, chest pain, dizziness, breathing difficulties, and fatigue), but overall most recorded episodes were asymptomatic (62.3% in the dronedarone group and 54% in the placebo group).
- Patients in the dronedarone group had a slightly lower heart rate (average 103 bpm) during their first recurrence than did those in the placebo group (average 117 bpm).
- Rates of thyroid, liver and lung dysfunction observed over the 12-month trial period were not significantly increased in the dronedarone group. However, there was a substantially higher incidence of elevated serum creatinine levels in the dronedarone group (2.4% vs. 0.2%), perhaps indicating potential problems with kidney function.
- At the end of the trial 22.8% in the dronedarone and 30.9% in the placebo group had been hospitalized or had died (death accounted for 1% in the dronedarone group and 0.7% in the placebo group).

The researchers conclude that dronedarone is significantly more effective than placebo in maintaining sinus rhythm and in reducing ventricular rate during an afib episode.


Editor’s comment: An effective, safe replacement for amiodarone would certainly be welcome, but short of comparing the two drugs directly, it is difficult to say whether dronedarone can fill this role.
Thus, recruitment for a trial to compare dronedarone and amiodarone is currently underway.

**Magnetically guided ablation not yet ready for prime time**

CLEVELAND, OHIO. In order to meet the rapidly growing demand for catheter ablations for atrial fibrillation, it is imperative that the procedure be made less dependent on operator skill and experience. Only by using procedures, which allow relatively inexperienced EPs to achieve a high degree of success, can this demand be met. There are basically three requirements for a successful ablation – mapping the atrium accurately so that the points or lines to be ablated can be determined; navigating the ablation catheter to the points determined in the mapping; creating lesions or lines at these points that are deep enough to ensure complete electrical disconnection. Mapping can be done effectively through electrical (potentials) or electroanatomic measurements, perhaps combined with an overlay of a CT scan or magnetic resonance image (MRI). Highly effective ablation catheters have also been developed with the open-irrigation tip catheter being the current favourite.

The main remaining challenge involves accurate navigation to the ablation sites. Currently used catheters are relatively stiff and, even in the most experienced hands, are often difficult to maneuver so as to achieve complete electrical isolation of the pulmonary veins. This has led to the recent development of highly maneuverable ablation catheters that are guided by external magnets and theoretically can reach any part of the atrium. As a further refinement these catheters can now be positioned at the ablation site by an operator situated in front of a computer screen in a room away from the actual operating room. The catheter can be manipulated by a special joystick (wand method) or by a combination of a joystick and a mouse (coordinate method).

Electrophysiologists at the Cleveland Clinic recently reported on their evaluation of the Niobe II magnetic navigation system (Stereotaxis). This system uses a radiofrequency-heated, 4-mm, solid-tip, magnetic ablation catheter. After familiarizing themselves with the system in a series of 48 AF patients the EPs did a formal study of the system on 45 afibbers (33% paroxysmal, 38% persistent, and 29% permanent) with an average age of 60 years (60% male). The ablation was performed in a step-wise fashion so that step 2 was only implemented if step 1 did not achieve total electrical isolation of the pulmonary veins, and step 3 was only undertaken if step 2 was not successful. The three steps were as follows:

- **Step 1** – Circumferential pulmonary vein isolation (Pappone method) of the right and left pulmonary veins using the Niobe II system and electroanatomical mapping.
- **Step 2** – Pulmonary vein antrum isolation (Natale method) using the Niobe II system, electroanatomical mapping and ICE guidance.
- **Step 3** – Pulmonary vein antrum isolation (Natale method) using fluoroscopy and ICE guidance and a 3.5-mm tip, open-irrigation catheter. This is the conventional protocol used at the Cleveland Clinic.

Although the Niobe II system was very successful in navigating the ablation catheter to the desired spots (60% success with coordinate method, 100% with wand method), electrical disconnection was only achieved in 4 veins in 4 different patients. In the remaining 41 patients (92%) no disconnection was observed in any veins. The step 3 approach (conventional method) was then applied to all patients in order to achieve isolation. In the first 23 patients all pulmonary veins were successfully disconnected, while in the remaining 22 patients only the right pulmonary veins were isolated (after failed attempts to isolate the left ones with the Niobe II system). After a mean follow-up of 11 months, 78% of the 23 patients who had achieved full isolation were afib-free as compared to only 10% in the group where only the right veins were successfully isolated.

The Cleveland researchers conclude that the Niobe II 4-mm tip ablation catheter is incapable of creating adequate lesions for a successful AF ablation. They also noted frequent charring (33% of patients) at the catheter tip, which could lead to thromboembolic complications (ischemic stroke).
Lindsay, BD. Is pulmonary vein antrum isolation a critical determinant of recurrent arrhythmias after ablation of atrial fibrillation? Journal of the American College of Cardiology, Vol. 50, August 28, 2007, pp. 875-76

Editor’s comment: The Niobe II (Stereotaxis) system is clearly effective in positioning the ablation catheter at any desired point in the left atrium using remote control. Unfortunately, the presently used catheter would seem to be ineffective in creating adequate lesions. Work is underway to develop an open-tip, irrigated catheter for use in the system. This would seem to be a formidable challenge, but if overcome could lead to a new, highly effective ablation protocol that could be used successfully by relatively inexperienced operators.

**Box isolation effective for paroxysmal AF**

FUKUOKA, JAPAN. There is substantial evidence that most paroxysmal afib episodes are initiated in and around the junctions of the pulmonary veins with the left atrium. However, the back (posterior) wall of the left atrium is also an important source of ectopics capable of initiating and sustaining full-blown AF. The three most common procedures (Haissaguerre, Pappone and Natale) all aim to isolate the pulmonary veins and may include additional lesions as required. A rare (1 in 1000), but very serious, complication of these procedures is the accidental burn-through to the esophagus creating an atrial esophageal fistula. The esophagus runs very close (2-4 mm away) to the posterior left atrial wall, so achieving complete isolation of the pulmonary veins without ablating close to it is often difficult.

Japanese electrophysiologists now report on their experience with a novel ablation procedure aptly named “Box isolation”. The initial purpose of the new technique was to avoid having to create vertical lesions in the neighborhood of the esophagus. Essentially, the procedure involves creating a box-like lesion set encompassing the pulmonary veins and indeed most of the posterior wall of the left atrium. Vertical lesions in the vicinity of the esophagus are avoided and extra precautions are taken when creating the top and bottom lines of the box where they cross the esophagus.

The procedure was evaluated in a group of 91 paroxysmal afibbers (95% with lone AF) who had suffered from afib for an average of 5 years and experienced, on average, 10 episodes a month. All had failed antiarrhythmic drug treatment. The ablation procedure was performed during AF (spontaneous or induced) in 93% of the patients. At the completion of the box isolation, AF could no longer be induced in 71% of the patients. Three months after the procedure 90% of the patients were free of afib without the use of antiarrhythmics. Repeat ablations were performed (three months after the first procedure) in 6 patients, and 13 months after the initial procedure 86 (95%) of the patients were free of afib without the use of antiarrhythmics. The remaining 5 patients were also afib-free, but only with the use of antiarrhythmic drugs.


Editor’s comment: Based on this relatively small sample size the Box isolation technique would appear to be highly effective (95% success) in primarily lone, paroxysmal afibbers. It is, however, doubtful that it would be equally effective in persistent and permanent AF where maintenance of afib may be related to other areas in the heart such as the superior vena cava, the base of the left atrial appendage, and the interatrial septum.

**Fish oils and arrhythmias**

PITTSBURGH, PENNSYLVANIA. Researchers at the National Institutes of Health and 10 major US hospitals and universities provide an excellent summary of the current knowledge regarding the benefits of omega-3 fatty acids in the prevention of cardiac arrhythmias. There is overwhelming evidence that an adequate intake of the long-chain omega-3 fatty acids eicosapentaenoic acid (EPA)
and docosahexaenoic acid (DHA) is highly protective against sudden cardiac death (SCD), which is caused by ventricular arrhythmias in 80-90% of cases. A high blood level of EPA and DHA was associated with an 81-90% reduction in SCD in a group of healthy people without known coronary heart disease. As little as 1 gram a day of EPA and DHA (found in oily fish and fish oils) has also been found to be highly protective against SCD in patients having suffered a previous heart attack. The American Heart Association now recommends that all adults consume fish, preferably fatty, at least twice a week, and that patients with coronary heart disease consume 1 gram a day of EPA and DHA combined.

The effect of oily fish consumption or fish oil supplementation on atrial fibrillation is less clear. One study involving 4815 men and women 65 years or older (mean age of 73 years) found that consumption of baked or broiled fish was associated with a significantly reduced risk (31%) of developing AF over a 12-year follow-up period. In contrast, a study involving 48,000 much younger people (mean age of 56 years) found an increased risk (34%) of AF with increased fish consumption over a 5.7-year follow-up period. A randomized trial of fish oil supplementation (850 mg EPA+DHA) prior to bypass surgery found that 15% of patients randomized to fish oil developed post-procedure AF as compared to 33.3% in the control group.

The researchers suggest that the reason for the discrepancy between the results of the trial involving older people and the one involving younger people could well be that fish oils tend to increase parasympathetic (vagal) tone and this could be detrimental in younger people, while it may be beneficial in older people where sympathetic (adrenergic) tone tends to dominate. Older people would also be more likely to have systemic inflammation and atrial fibrosis which may be reduced by a high intake of long-chain omega-3 fatty acids.

Dietary supplementation with long-chain omega-3 fatty acids (fish oils) is known to change the composition of lipid membranes toward greater fluidity. There is also evidence that fish oil supplementation inhibits a number of sodium, potassium and calcium channels in a beneficial way and reduces the production of pro-inflammatory thromboxanes – all actions that could reduce the incidence of cardiac arrhythmias.


Editor’s comment: The authors of this very detailed and highly technical report are clearly convinced that long-chain omega-3 fatty acids (EPA and DHA) play a crucial role in reducing the risk of sudden cardiac death and possibly atrial fibrillation. They propose several research projects to investigate this further – hopefully the harbinger of a trend to consider diet and dietary components as important factors in the development and maintenance of AF.