THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation!

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An average, medium-term, complete success rate (no afib, no antiarrhythmics) of 80% is generally considered very high indeed even for relatively uncomplicated initial catheter ablations for the purpose of curing AF in paroxysmal afibbers. Now Japanese electrophysiologists report that success rates as high as 92% can be achieved simply by re-ablating conduction gaps making their appearance during a 90-minute wait period following the "official" completion of the pulmonary vein isolation procedure. Electrophysiologic measurements made at the start of repeat procedures have clearly shown that the need for a second procedure is almost entirely due to the appearance of electrically conductive gaps in the original lesion rings. The Japanese study would indicate that most of these reconnections occur within a 90-minute period following the end of the procedure. Thus, it would make imminent sense to add 90 minutes to initial ablations for the purpose of doing the isoproterenol/ATP challenges as outlined by the Japanese researchers.

Also in this issue we report that even multiple catheter ablations do not appear to impair left atrial function, that post-ablation therapy with corticosteroids decrease the risk of early AF recurrence, that an apple a day keeps stroke away, and that vitamin C is highly effective in preventing heart failure.

And 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.

Wishing you lots of NSR,

Hans

Highlights

Diabetes drug metformin implicated in AF

KANSAS CITY, KANSAS. Metformin (glucophage) is a widely used drug for the treatment of type 2 diabetes. It is relatively benign but is associated with a serious, but rare side effect called lactic acidosis, a condition in which lactic acid builds up in the blood stream faster than it can be eliminated and thereby creates an acidic milieu in the body. Lactic acidosis can also result from intense exercise and impaired kidney function.

A group of cardiologists from the University of Kansas Hospital and Medical Center now reports that case of a 68-year-old man who developed atrial fibrillation (AF) as a result of treatment with metformin. The patient had normal liver and kidney function, but did suffer from hypertension, type 2 diabetes, anxiety disorder, and coronary heart disease, and was on 6 different medications. At a follow-up visit with his primary physician his prescription for sitagliptin (Januvia), an oral anti-diabetic drug, was replaced with one for metformin. Seventy-two hours after taking the first dose of the new drug, the patient reported to the emergency department with AF. He reported a similar episode in the past when he was on metformin, which resolved when he discontinued the drug.

After arriving in the ER the metformin was discontinued and the patient converted to normal sinus rhythm (NSR) on his own after 48 hours. Once in NSR he was rechallenged with metformin and once again – 48 hours later – went into AF. NSR was restored 48 hours after discontinuing the metformin.

The Kansas cardiologists confirmed a build-up of lactate during metformin administration and conclude that the patient developed lactic acidosis subsequent to metformin administration and that this, in turn, caused a bout of AF.

Boolani, H, Lakkireddy, et al. Metformin associated atrial fibrillation – a case report. **Journal of Atrial Fibrillation**, *Vol. 2, No. 7, September 2011*

Editor's comment: Although lactic acidosis is a rare side effect of metformin usage, afibbers using the drug should clearly keep an eye out for possible metformin-induced episodes, especially if their kidneys are functioning less than optimally.

Liver failure associated with dronedarone

MUNICH, GERMANY. Dronedarone (Multaq) was introduced in 2009 as a safe and effective alternative to amiodarone which, although highly effective, has a substantial number of serious adverse effects. Dronedarone and amiodarone have similar molecular structures except that the iodine moiety in amiodarone has been replaced by a methane sulfonamide group in dronedarone. Both drugs maintain the main structure of benzofuran, a structure that in animal experiments has been associated with liver damage.

Now a group of German researchers from the Technical University of Munich reports the case of a 70-year-old woman who was admitted to the university's hospital with fatigue and jaundice (increased level of bilirubin in the blood). Her liver tests had been normal 9 months prior to admission, but 6 months prior to admission she had been prescribed dronedarone for atrial fibrillation (AF). The patient was a non-smoker and did not drink alcohol, but she was on 9 different prescription drugs. Over the course of her hospital stay her bilirubin level peaked at a dangerously high 30.3 mg/dL and she was diagnosed with dronedarone-induced acute liver failure. She underwent a liver transplant 11 days later and, after a critical first week, recovered completely during the following 10 weeks. Autopsy of her diseased liver detected widespread necrosis of liver acini and other massive damage.

The German researchers conclude that regular monitoring of liver function is a must for patients on dronedarone (Multaq). They also point out that liver problems occurred in 12% of patients involved in the original clinical trials of dronedarone.

Joghetaei, N, Estner, H, et al. Acute liver failure associated with dronedarone. **Circulation: Arrhythmias and Electrophysiology**, *Vol. 4, 2011, pp. 592-93*

Editor's comment: Unfortunately, this report is not the first pointing to a less than sterling safety profile for dronedarone. On September 22, 2011 the European Medicines Agency (EMA) issued a bulletin recommending restricting the use of dronedarone to cases where no other drugs had proven effective. This recommendation was partly based on the results of the prematurely-halted PALLAS trial which observed an increased risk of cardiovascular events in patients treated with the drug. The EMA recommends that dronedarone use should be restricted to patients with paroxysmal or persistent AF when they are in normal sinus rhythm. It should not be used when patients are in AF, nor in those with permanent AF or heart failure. In any case, patients on the drug should be monitored by a specialist and have their lung, liver and heart rhythm function checked regularly.

Several electrophysiologists have expressed their misgivings about the drug. Dr. Steven Nissen of the Cleveland Clinic believes dronedarone is outright dangerous and Dr. Sanjay Kaul of Cedar-Sinai Medical Center in Los Angeles says that the drug does not even appear to be safe in intermediate-risk patients.[1] It seems to me that giving paroxysmal afibbers a drug that becomes dangerous whenever they actually experience AF is a less than smart move. I think dronedarone deserves a place, alongside digoxin and sotalol, as the most useless pharmaceutical drug for lone AF patients.

[1] http://www.theheart.org/article/1283205/print.do

Post-ablation corticosteroid therapy

HARTFORD, CONNECTICUT. There is ample evidence that myocardial inflammation is a common sequel to radiofrequency (RF) catheter ablation for the purpose of curing atrial fibrillation (AF). It is also well established that as many as 40% of patients undergoing RF ablation experience early recurrence of AF before they even leave the hospital following their procedure. Early recurrence, in turn, has been linked to a poorer long-term outcome.

A group of electrophysiologists at the Hartford Hospital in Connecticut now report that treatment with intravenous antiinflammatory agents (corticosteroids) immediately after RF ablation and for the following 48 hours substantially reduce the incidence of early recurrence. Their study included 68 patients with paroxysmal (56%) or persistent (44%) AF most of whom had no underlying heart disease. The patients all underwent an anatomically-guided pulmonary vein isolation procedure with concomitant use of electrophysiologic mapping. Thirty-seven patients received 6 intravenous injections each containing 4 mg of dexamethasone over a 48-hour period post-ablation with the first injection given within 6 hours following completion of the procedure. Another 31 patients (control group) received no post-procedure corticosteroids or other antiinflammatories. All patients also received antiarrhythmics following the procedure.

During the hospital stay (an average of 3 days), 16 patients (23.5%) experienced an early recurrence of AF defined as an episode lasting longer than 10 minutes. Patients who had received dexamethasone had an 82% reduction in their odds of experiencing early recurrence. For each milligram of dexamethasone equivalent administered a 17% reduction in the odds of experiencing early recurrence occurred. Older age and prior use of digoxin, on the other hand, were found to increase the likelihood of early recurrence, while type of AF (paroxysmal or persistent) did not affect the odds of experiencing early recurrence.

The authors conclude that the administration of intravenous dexamethasone post-ablation substantially reduces the risk of early recurrence of AF and may result in an improved long-term outcome.

Sood, NA, Clyne, CA, et al. Intravenous corticosteroid use is associated with reduced early recurrence of atrial fibrillation immediately following radiofrequency catheter ablation. **Journal of Atrial Fibrillation**, *Vol. 2, No. 7, September 2011*

Editor's comment: A group of researchers from the University of California (San Francisco) found that ablatees with early recurrence were 21 times more likely to have elevated levels of C-reactive protein, a powerful indicator of inflammation, than were patients with no early recurrence.[1] Thus, it clearly makes sense to make a concerted effort to deal with post-ablation inflammation. A recent randomized trial reported by a group of Japanese researchers concluded that post-ablation corticosteroid therapy decreased the incidence of both early (7% vs 31%) and 14-month recurrence (29% vs 15%) in a group of 125 paroxysmal afibbers randomized to corticosteroid (hydrocortisone and prednisolone) therapy or placebo.[2]

[1] McCabe, JM, et al. Protracted CRP elevation after atrial fibrillation ablation. Pacing and Clinical Electrophysiology, Vol. 31, 2008, pp. 1146-51

[2] Koyama, T, et al. Prevention of atrial fibrillation recurrence with corticosteroids after radiofrequency catheter ablation. Journal of the American College of Cardiology, Vol. 56, 2010, pp. 1463-72

Vitamin C helps prevent heart failure

CAMBRIDGE, UNITED KINGDOM. Although not related to lone atrial fibrillation (AF), I found a recent study linking a higher plasma level of vitamin C to a lower risk of heart failure to be of sufficient interest to include in this issue of the newsletter.

The recently reported study involved 9,187 men and 11,112 women aged between 39 and 79 years and apparently healthy when enrolled in the European Prospective Investigation into Cancer and Nutrition between 1993 and 1997. During a follow-up period of 12.8 years, 154 fatal and 1,104 non-fatal cases of heart failure were reported involving 724 men and 534 women (incidence 0.5%/person-year). The researchers involved in the study discovered a clear correlation between the incidence of heart failure and a low plasma level of vitamin C. An increase of 20 micromol/L in plasma vitamin C concentration was associated with a 17% relative reduction in risk of heart failure. They believe the plasma level of

vitamin C reflects intake of fruits and vegetables, but found no correlation between self-reported intake of fruit and vegetables and the risk of heart failure.

The study clearly showed the benefits of high plasma vitamin C levels. An average level of 70 micromol/L (quartile 4) was associated not only with a decreased risk of heart failure, but also with a statistically highly significant lower body mass index, waist-hip ratio, systolic blood pressure, diastolic blood pressure, total cholesterol, glucose level, and C-reactive protein (an important marker of inflammation) level when compared to an average plasma level of 23 micromol/L. A high vitamin C plasma level was also associated with a significantly reduced risk of hypertension and diabetes.

A higher occupational social class, greater physical activity, and a higher level of education were all associated with a higher plasma vitamin C level indicating that these factors are important in living a healthy lifestyle, which would tend to include an increased intake of vitamin C both in the form of fruits and vegetables, and in the form of vitamin C supplements. NOTE: 12% of the group constituting quartile 4 was supplementing with vitamin C as compared to only 1% in quartile 1.

The researchers conclude that every 20 micromol/L increase in plasma vitamin C concentration is associated with a 9% relative risk reduction in the risk of heart failure after adjusting for age, sex, smoking, alcohol consumption, physical activity, occupation social class, educational level, systolic blood pressure, diabetes, cholesterol level, body mass index, and interim coronary heart disease.

Pfister, R, Khaw, KT, et al. Plasma vitamin C predicts incident heart failure in men and women in European Prospective Investigation into Cancer and Nutrition – Norfolk prospective study. **American Heart Journal**, *Vol. 162, No. 2, August 2011, pp. 246-53*

Editor's comment: This study adds to the already abundant evidence that an adequate intake of vitamin C is essential for the maintenance of health and the avoidance of disease. See www.yourhealthbase.com/database/rvitamin_C.htm www.yourhealthbase.com/category/vitaminc.htm. Unfortunately, the average daily intake of vitamin C in the USA and Canada is only about 60 mg, which is unlikely to yield an optimum plasma level. A daily intake of 200 mg/day, on the other hand, would likely result in a plasma level of 90 micromol/L corresponding to an almost 30% decrease in the risk of heart failure. By supplementing with 1250 mg/day (in divided doses) a peak plasma vitamin C level of 187 micromol/L can be achieved. See www.yourhealthbase.com/database/a151d.htm

Single ablation success rate of 92%!!

TOKYO, JAPAN. Between 20 and 50% of atrial fibrillation (AF) patients undergoing a pulmonary vein isolation (PVI) procedure requires one or more follow-up procedures in order to achieve the goal of remaining in normal sinus rhythm long-term without the use of antiarrhythmics. AF recurrence is almost always due to electrical reconnection between the left atrium and the once isolated pulmonary veins. Japanese researchers have found that injecting an isoproterenol solution and ATP (adenosine-5'-triphospate) 20 minutes after completion of the PVI will reveal dormant gaps in the lesion rings encircling the pulmonary veins. Re-ablating these gaps can markedly improve long-term success rates, especially for paroxysmal afibbers.

Now the same group of researchers report that medium-term success rates for single ablations involving paroxysmal afibbers can be improved to 92% by injecting the isoproterenol/ATP solution 30, 60 and 90 minutes after first achieving complete electrical isolation between the pulmonary veins and the left atrium. Their study involved 75 paroxysmal afibbers (92% men, average age 55 years, average duration of AF 4.5 years). Thirty-five patients had heart disease and 20 had hypertension.

All patients underwent a PVI procedure using the double Lasso technique with accompanying CARTO electroanatomical mapping. Thirty minutes after a bidirectional conduction block had been established between the left atrium and the pulmonary veins, the double Lasso catheters were used to check if gaps had developed in the lesions rings. Seventy-five gaps were found in 37 patients. These gaps were successfully re-ablated whereupon the isoproterenol/ATP solution was injected and the search for gaps repeated. This time 76 gaps were found and successfully re-ablated. The above procedure was repeated 60 minutes after the completion of the initial PVI procedure. This time 64 new gaps were found and re-ablated. After injection of the isoproterenol/ATP

solution, another 36 gaps appeared and were re-ablated. Finally, 90 minutes after the completion of the initial PVI, another 8 gaps were found and successfully re-ablated. Total average procedure time was about 3 hours including the 90-minute post-procedure wait time.

At the mean follow-up of one year (370 days) only 6 patients (8%) had experienced recurrence of AF resulting in a medium-term success rate of 92%.
Yamane, T, Yoshimura, M, et al. Repeated provocation of time- and ATP-induced early pulmonary vein reconnections after pulmonary vein isolation: eliminating paroxysmal atrial fibrillation in a single procedure. **Circulation: Arrhythmias and Electrophysiology**, *August 13, 2011 [Epub ahead of print]*

Editor's comment: A medium-term, complete success rate (no AF, no antiarrhythmics) of 92% for a single ablation is astonishing and would appear to be readily achievable for paroxysmal afibbers by using a combination of wait time and isoproterenol/ATP injection to reveal gaps that develop in initially intact lesion rings over a period of 60 to 90 minutes after completion of the PVI procedure.

Left atrial function following repeat ablations

BARCELONA, SPAIN. A radiofrequency catheter ablation for atrial fibrillation (AF) creates a significant amount of scar tissue. An important question is does this scar tissue impair the function of the left atrium? Although the function of the left atrium is mainly to act as a reservoir for the left ventricle, it does contribute some pumping action on its own and a significant reduction in this action may have undesirable consequences. Prior research has shown that the volume of the left atrium tends to shrink after a first ablation (a beneficial effect) and that the contractile function is not impaired. NOTE: Contractile function is assessed as the active emptying percentage of the total left atrial volume.

Electrophysiologists at the University of Barcelona now confirm the above findings. Their study included 154 patients with symptomatic, drug-refractory AF. The majority (78%) of the patients were men, average age was 53 years, and average time since diagnosis was 5 years. Half of the study participants had paroxysmal AF, 36% had persistent AF, while the remaining 14% had been in AF for more than a year (permanent AF). Prior to their scheduled ablation and 6 months post-ablation, all patients had their left atrial volume and active emptying percentage measured using real-time, 3-dimensional echocardiography.

All patients underwent an anatomically-guided (CARTO) pulmonary vein isolation procedure with an additional left atrial roof line in the case of persistent and permanent afibbers. Patients were followed at 1, 3 and 6 months to evaluate recurrence. At the 6-month follow-up, 54% of patients having undergone a single procedure were in normal sinus rhythm (NSR), while only 40% of the 50 patients who underwent a second procedure were in NSR. Patients in the single ablation group who experienced recurrence after 6 months (mostly persistent afibbers) had a significantly larger left atrial volume prior to their ablation than did those who were in NSR at 6 months post-ablation.

Maximum left atrial volume was reduced from a baseline average of 60 to 52 mL and a minimum volume from 38 to 32 mL after a first ablation. Reductions after a second procedure were from 57 to 52 mL (maximum volume) and from 37 to 35 mL (minimum volume). Contractile function (active emptying percentage) did not change significantly (39% vs 43%) after a first or second procedure (36% vs 36%). The Spanish researchers conclude that the contractile function of the left atrium is not deleteriously affected even after repeat ablations, and that radiofrequency catheter ablations result in a beneficial shrinking of the left atrium.
Montserrat, S, Brugada, J, et al. Effect of repeated radiofrequency catheter ablation on left atrial function for the treatment of atrial fibrillation. **American Journal of Cardiology**, *Sept. 8, 2011 [Epub ahead of print]*

Editor's comment: Many afibbers have expressed concern about the effect of one or more radiofrequency ablations on the function of the left atrium. This study provides reassuring proof that such concerns are unwarranted.

An apple a day keeps stroke away!

WAGENINGEN, THE NETHERLANDS. There is ample evidence that a high consumption of fruits and vegetables lowers the risk of stroke. What is not known is whether some fruits and vegetables are more effective in stroke prevention than others. A group of researchers from Wageningen University now answers this question.

Their study included 20,069 men and women between the ages of 20 and 65 years who were free of cardiovascular disease at baseline. During 10 years of follow-up, 226 nonfatal and 19 fatal strokes were recorded (0.11%/year). It is worth noting that 12 of the patients who suffered a fatal stroke had previously had a nonfatal stroke. The majority (60%) of the strokes was ischemic, 19% were hemorrhagic, and the remaining 21% were of unknown origin. All participants completed a validated, self-administered food-frequency questionnaire at enrolment between 1993 and 1997.

Fruit and vegetable intake was grouped according to the predominant colour of the produce. Thus, the green colour group consisted of broccoli, brussel sprouts, cabbage, kale, spinach, endive, and lettuce. The orange/yellow group included citrus fruit, cantaloupe, carrot, carrot juice, and peach. The red/purple group contained red beets, red cabbage, cherries, grapes, strawberries, red sweet pepper, tomato, and tomato juice. The white group consisted of garlic, leeks, onion, apples (including apple sauce and apple juice), pears, banana, cauliflower, chicory, cucumber, and mushrooms.

The average daily fruit and vegetable intake was 378 grams/day with white fruits and vegetables contributing 36%, and orange/yellow fruits and vegetables contributing 29% of total intake. Apples and pears constituted 55% of the white fruit and vegetable intake, while citrus fruits accounted for 78% of the orange/yellow group. After adjustment for lifestyle and other dietary factors, the researchers concluded that study participants whose intake of white fruits and vegetables exceeded 171 grams/day had halved their stroke risk as compared to those whose intake was 78 grams/day or less. Thus, a 25-gram/day increase in the intake of white fruits and vegetables corresponds to a 9% (relative) reduction in the risk of stroke. NOTE: In this study apples and pears constituted 55% of the total daily intake of white fruits and vegetables.

Consumption of green, orange/yellow and red/purple fruits was not associated with a decreased stroke incidence. The Dutch researchers point out that apples are a rich source of quercetin (3.6 mg/100 grams) and dietary fiber (2.3 grams/100 grams) and that other researchers have found that a high intake of flavonoids like quercetin is associated with a 20% reduction in stroke risk.

Oude Griep, LM, Geleijnse, JM, et al. Colors of fruit and vegetables and 10-year incidence of stroke. **Stroke**, *Vol. 42, November 2011*

Effectiveness of ablations in athletes

LEUVEN, BELGIUM. There is sufficient evidence that endurance athletes are far more likely to develop lone atrial fibrillation (LAF) than are more sedentary people (www.afibbers.org/resources/endurancesports.pdf). However, it is not clear whether a LAF condition associated with endurance sports responds differently to catheter ablation for the purpose of curing atrial fibrillation (AF). Researchers at the University of Leuven now provide an answer to this question.

Their study included 94 athletes and a matched control group of non-athletes (sedentary persons) with AF (90% paroxysmal and 10% persistent). Mean age was 51 years, and AF symptoms had been present for a median of 4 years prior to the initial ablation. The athlete group was divided into two groups – group 1 consisted of 59 endurance athletes with an average lifetime (since age of 14) number of sports practice hours of 10,550, while group 2 consisted of 35 non-endurance athletes with an average lifetime sports practice hours of 3,450. The average lifetime sports practice hours in the control group was 450. Endurance training involved running, cycling, swimming or rowing.

All study participants underwent a pulmonary vein isolation (PVI) procedure using electrophysiologic (Lasso catheter and fluoroscopic guidance)

mapping using an irrigated-tip catheter. Roof lines were applied as required and 80% of patients also underwent a right atrial flutter (cavo-tricuspid isthmus) ablation. Patients were followed up with ECGs and Holter monitoring at 6 weeks, 6 months and 1 year, and yearly thereafter. Recurrences during the first 6 weeks post-ablation were not counted.

Three years after the initial ablation, 52% of controls, 54% of endurance athletes, and 66% of non-endurance athletes had experienced one or more AF recurrences. Twenty-seven (20%) of ablatees underwent follow-up procedures. Three years after the final procedure, 63% of the control group were in normal sinus rhythm (NSR) without the use of antiarrhythmic drugs, while 24% managed to remain afib-free with the aid of previously ineffective antiarrhythmics (Class II or II). Corresponding numbers for endurance and non-endurance athletes were 54% and 30%, and 40% and 45% respectively.
Overall success rates (no AF with or without the aid of antiarrhythmics) were thus 87% for the control group, 84% for endurance athletes, and 85% for non-endurance athletes. The Belgian researchers conclude that having been a lifelong endurance athlete does not decrease the chance of achieving freedom from AF following one or more PVI procedures.

Koopman, P, Heidbuchel, H, et al. Efficacy of radiofrequency catheter ablation in athletes with atrial fibrillation. **Europace**, *Vol. 13, 2011, pp. 1386-93*

Editor's comment: For most afibbers a successful PVI procedure is one that results in complete freedom from AF and other tachycardia episodes without the use of antiarrhythmic drugs. Using these criteria as indicators of complete success, actual 3-year success rates after final ablation become:

Control group	63%
Endurance athletes	54%
Non-endurance athletes	40%

The differences in the above percentages are not statistically significant.

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