THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation!

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Almost 20 years ago, Rodney Falk MD, a leading electrophysiologist at Boston City Hospital, made the following statement about digoxin:

"Studies now suggest that in patients with atrial fibrillation, digoxin is a poor drug for controlling heart rate during exertion, has little or no effect in terminating the arrhythmia, and may occasionally aggravate paroxysmal atrial fibrillation".

Fifteen years ago, Philippe Coumel MD, a world-renowned expert on atrial fibrillation said:

"Not only are beta-blockers or digoxin not indicated in vagal atrial fibrillation, but they are definitely contraindicated as they tend to promote the arrhythmia and may block the action of conventional antiarrhythmic treatment".

More recently, researchers have found that digoxin may turn paroxysmal afib into the permanent form, may cause visual disturbances, increases the risk of breast cancer, and aggravates asthma attacks. As if this was not enough, Swedish researchers recently reported that digoxin prolongs afib episodes, interferes with electrical cardioversion, and doubles the risk of otherwise healthy afibbers dying within a year after having been prescribed digoxin. Simply put, digoxin should never be prescribed to or taken by lone afibbers.

In this issue, I update my original article "Digoxin: The Medicine From Hell?" in the hope that it may further reduce the unwarranted and dangerous use of digoxin among lone afibbers. Also in this issue, we confirm that MSG and aspartame may precipitate afib episodes, that systemic inflammation may be a common factor for AF and kidney disease, that air pollution affects INR values, and we present new data that extreme endurance sports are a potent risk factor for lone AF.

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

Association between kidney disease and AF

KURASHIKI CITY, OKAYAMA, JAPAN. The main function of the kidneys is to remove excess water and waste products from the blood. The kidneys process about 200 liters of blood and produce about 2 liters of urine every day. An indication of the health of the kidneys can be obtained by evaluating their filtration capacity. An estimated glomerular filtration rate (GFR) above 60 mL/min is usually considered a sign of good kidney function, while a

rate below 45 mL/min may indicate chronic kidney failure (CKF). The calculation of GFR is primarily based on the serum creatinine level, but also takes into account results of urine tests, age, gender, and other factors. An adequate kidney function is particularly important for afibbers supplementing with potassium and magnesium since any excess of these vital electrolytes are excreted by the kidneys.

Japanese researchers now report an association between GFR and atrial fibrillation. Their study involved 41,417 citizens (13,956 men) of Kurashiki City who underwent a health-screening test. About 35% of the participants were found to have hypertension, while about 9% had cardiovascular disease. During the medical examination, 676 study participants (1.6%) were found to have atrial fibrillation. Obviously, the real prevalence of afib in the group may have been significantly higher since all cases of paroxysmal afib would not have been picked up by one single electrocardiogram.

The researchers observed a significant inverse correlation between the prevalence of afib and GFR. Thus, the prevalence of afib in the one-third (lower tertile) of participants having an average GFR of 54 mL/min (more specifically 54 mL/min per 1.73 m^2) was 2.8% as compared to only 0.9% in the group (high tertile) having an average GFR of 84 mL/min. Not surprisingly, the incidence of afib also increased with age.

The Japanese researchers speculate that the common factor between AF and reduced GFR (kidney disease) is systemic inflammation and suggest that ACE inhibitors and angiotensin receptor blockers may be helpful in preventing both conditions.

Iguchi, Y, et al. Relation of atrial fibrillation to glomerular filtration rate. **American Journal of Cardiology**, *Vol. 102, 2008, pp. 1056-59*

Editor's comment: The findings of this study again emphasize the importance of avoiding systemic inflammation. Fortunately, there are many natural anti-inflammatories that will effectively combat inflammation – *Zyflamend*, beta-sitosterol, bromelain, curcumin, boswellia, *Moducare*, quercetin, and fish oil.

AF precipitated by MSG and aspartame

SYLVANIA, OHIO. At least two of our LAF surveys have found that a significant proportion of lone afibbers are sensitive to the food flavour enhancer MSG (monosodium glutamate) and the artificial sweetener aspartame (NutraSweet, Equal, Canderel). Now a researcher at the University of Toledo College of Medicine confirms this connection. Dr. Craig Burkhart describes the case of a 57-year-old physician (no underlying heart disease or hypertension) who was diagnosed with persistent atrial flutter, which was resolved in 2007 with a catheter ablation. However, over the next several months the patient developed paroxysmal atrial fibrillation. While awaiting a second ablation, he decided to eliminate MSG and aspartame from his diet and experienced an immediate elimination of his afib episodes. To test the validity of this finding, he challenged himself on three separate occasions with MSG (Chinese food and beef jerkies) and with aspartame in the form of a diet soft drink. All of these challenges resulted in afib episodes within a few hours.

Dr. Burkhart points out that the reaction to MSG and aspartame is likely caused by the release of their metabolites, glutamate and aspartate during digestion. Both of these chemicals are strong excitotoxins, which excite not only brain tissue, but also cardiac tissue. They have been associated with numerous symptoms including headaches, dizziness, seizures, nausea, numbness, muscle spasms, fatigue, heart palpitations, anxiety attacks, vertigo, and memory loss. He concludes that this case history adds further credence to the idea that eliminating MSG and aspartame from the diet may be beneficial for some patients with atrial fibrillation.

Burkhart, CG. 'Lone' atrial fibrillation precipitated by monosodium glutamate and aspartame. **International Journal of Cardiology**, *February 9, 2009 [Epub ahead of print]*

Editor's comment: Our first LAF survey (February 2001) found that 10% of respondents experienced afib episodes after ingestion of MSG, while 4% did so following ingestion of aspartame. A later, significantly larger survey (LAFS-14) found that 22% of afibbers who had eliminated MSG from their diet had observed a better than 50% reduction in their episode frequency. Similarly, 24% of afibbers who had eliminated aspartame had found this to be highly beneficial. It is interesting that this article in the *International Journal of Cardiology* makes

mention of "The AFIB Report" in the following sentence:

> *The AFIB Report found that 10% of patients with atrial fibrillation found MSG and 4% listed aspartame as triggers for their attacks*.

Air pollution and INR

VERONA, ITALY. Many afibbers taking warfarin (Coumadin) for stroke prevention experience problems keeping their INR (International Normalized Ratio) within the prescribed range of 2.0 to 3.0. Diet, especially the intake of vegetables with dark, green leaves (excellent sources of vitamin K), can markedly affect INR and, according to a recent study carried out by a team of Australian and Italian researchers, so can air pollution.

Air pollution is a multi-headed beast. It is basically a heterogeneous mixture of solid and liquid particles suspended in air. Some common sources are car emissions, road dust, tire abrasion, power generation, pollen, moulds, and forest fires. The effects of air pollution on humans include inflammation, oxidative stress, dysfunction of the autonomic nervous system, adverse cardiovascular events, and inappropriate activation of the body's blood clotting mechanism. There is now evidence that even short-term exposure to air pollution, particularly diesel exhaust fumes and ultra-fine particles (less than 2.5 micrometers in diameter) can result in hypercoagulability (accelerated blood clotting), and thus increase the risk of ischemic stroke. Exposure to diesel exhaust has been found to increase the blood level of fibrinogen and plasminogen activator inhibitor-1, while decreasing the level of plasminogen activator. These changes all decrease prothrombin time (the measurement expressed as INR) and thus accelerate clot formation. Furthermore, there is also evidence that ultra-fine particles induce platelet accumulation, adding yet another potential stroke risk factor to the picture.

The Australian/Italian research team conclude that the extent of air pollution in an area may significantly affect not only actual clotting tendency, but also the results of the INR test – air pollution would presumably lower the value. They suggest that such factors as ethnicity, smoking, diet, exercise, and air pollution should be taken into account when interpreting INR results, but concede that this is unlikely to become common practice any time soon.

Lippi, G, et al. Air pollution and coagulation testing: a new source of biological variability? **Thrombosis Research**, *Vol. 123, 2008, pp. 50-54*

Ablation versus antiarrhythmics

BORDEAUX, FRANCE. Although the success of antiarrhythmic drugs in the treatment of atrial fibrillation (AF) leaves a lot to be desired, it is generally accepted that therapy with 2 or more antiarrhythmics should be tried before catheter ablation is considered. A group of electrophysiologist from Australia, Canada, France and the United States now question the wisdom of continuing to try additional, different antiarrhythmics in patients who have already failed at least one such drug.

Their clinical trial involved 112 patients with paroxysmal AF (average age of 51 years, 16% women). Most (74%) had lone AF with an average (median) of 12 episodes per month lasting an average of 5.5 hours each (median). After a through medical evaluation at enrolment, the study participants were randomized into a catheter ablation (CA) group and an antiarrhythmic drug (AAD) group. Patients in the CA group underwent a standard PVI with right atrial flutter ablation and additional lesion lines as required. Up to two additional ablations were allowed within the 3 months following the initial procedure. The overall repeat rate was 80% and the rate of major complications was 1.9% (tamponade and stenosis).

Patients in the AAD group were allowed to try up to 3 different drugs during the 3 months following enrolment and were then left on the last drug tried for the remaining 9 months of the 1-year study period unless they elected to undergo an ablation after the first 3 months of trying unsuccessful antiarrhythmics (63% did so after about 6 months). Prior to enrolment, flecainide and beta-blockers

were the most commonly used drugs followed by sotalol and propafenone. During the study, amiodarone was tried for the first time by 18 patients in the AAD group and failed in 12 (66%) of these patients.

All patients were monitored with 12-lead ECGs and 24-hour Holter recordings at 3, 6 and 12 months following enrolment. Any afib episode lasting longer than 3 minutes, whether picked up during monitoring or reported by the patients, was considered a treatment failure. At the end of the study (12 months after enrolment), 89% of the participants of the CA group were afib-free without the use of antiarrhythmics. In contrast, only 23% of those in the AAD group were free of afib at the end of the study and they, of course, were still taking antiarrhythmic drugs on a daily basis. The researchers observed that afibbers with a higher left ventricular ejection fraction at enrolment were more likely to have a successful ablation than were those with a lower ejection fraction (65% vs. 56%). An evaluation of exercise capacity and quality of life at the 12-month mark showed significantly greater improvement in the CA group than in the AAD group.

The authors conclude that CA is superior to further AAD treatment in patients who have previously taken and failed antiarrhythmics. NOTE: Nine of the 14 EPs reporting on the trial have financial ties to ablation catheter manufacturers.

Jais, P, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation. **Circulation**, *Vol. 118, December 9, 2008, pp. 2498-2505*

Callans, DJ. Apples and oranges: comparing antiarrhythmic drugs and catheter ablation for treatment of atrial fibrillation. **Circulation**, *Vol. 118, December 9, 2008, pp. 2488-90*

Editor's comment: Our LAF surveys have found generally poor efficacy of antiarrhythmic drug therapy. This study certainly confirms those findings. The seemingly inescapable conclusion is that if antiarrhythmics do not work after the first or, at the most, the second try, get in line for an ablation. An exception to this is if the drug prescribed was a beta-blocker. Beta-blockers do not prevent afib episodes they merely reduce the heart rate during an episode. Furthermore, vagal afibbers prescribed beta-blockers can expect their condition to worsen and may well succeed in eliminating their episodes altogether by discontinuing these drugs.

Afib and sports – once again!

BARCELONA, SPAIN. The team of Lluis Mont, Roberto Elosua and Josep Brugada of the University of Barcelona are tirelessly trying to get their message across – "extreme endurance sports practice is a potent risk factor for lone atrial fibrillation (LAF)". "Extreme" is usually defined as any sports activity (marathon running, cycling, swimming, jogging) that achieves a significantly elevated heart rate, lasts more than 45 minutes a session, and is performed regularly. It is estimated that 2 to 10% of the population now suffers from LAF and that about 30% of patients showing up in doctors' offices with paroxysmal AF are diagnosed with LAF. LAF is commonly associated with atrial flutter. The Spanish researchers quote the following studies to support their point:

- In 1998 Karjalainen and colleagues in Finland reported that the incidence of LAF (after 10 years of follow-up) was 5.3% in a group of elite orienteers versus 0.9% in the control group.

- Mont and colleagues at the University of Barcelona found that men engaging in vigorous, long-term sport practice were 5 times more likely to be diagnosed with LAF than were those in the general population. They also noted that there seemed to be a threshold of about 1500 lifetime hours of endurance sports after which the risk of LAF increased dramatically.

- The Barcelona team also studied a group of individuals who ran the Barcelona Marathon in 1990 and compared the incidence of LAF in this group with that in a group of more sedentary individuals. They found that the sportsmen were 4 times more likely to develop LAF over the 10-year follow-up period than were the more sedentary ones.

- A Swiss research team investigated 64 former Swiss professional cyclists who completed the Tour de Suisse at least once during the years 1955 to 1975. The cyclists (average age of 66 years) were compared with a group of age, weight, and hypertension presence matched golfers. The cyclists had a considerably lower heart

rate and an incidence of LAF and atrial flutter of 10% as compared to 0% among the golfers.

- Heidbuchel et al. at the University of Leuven in Belgium observed that endurance athletes have a significantly higher risk of developing LAF after a common flutter ablation.

Mont et al. make a few other salient comments in their study:

- Physical activity may increase atrial and ventricular ectopy and there is evidence that this increased ectopy in elite athletes may be reversed by detraining.

- Elite athletes have increased vagal tone, which has been found to shorten the atrial refractory period, creating the conditions for re-entry.

- There is evidence that excessive endurance exercise and overtraining can lead to chronic system inflammation and there is a relationship between LAF and elevated CRP level (an inflammatory marker).

- There is some evidence that endurance athletes have larger left atria and significant evidence of fibrosis.

The Mont team makes the following critical comments:

> *The typical clinical profile of sport-related AF or atrial flutter is a middle-aged man (in his forties or fifties) who has been involved in regular endurance sport practice since his youth (soccer, cycling, jogging, and swimming), and is still active. This physical activity is his favourite leisure time activity and he is psychologically very dependent on it. The AF is usually paroxysmal with crisis, initially very occasional and self limited, and progressively increasing in duration. Characteristically, AF episodes occur at night or after meals. As many as 70% of patients may suffer predominantly vagal AF. They almost never occur during exercise. This makes the patient reluctant to accept a relationship between the arrhythmia and sport practice, particularly since his physical condition is usually very good. The crises typically become more frequent and prolonged over the years and AF becomes persistent. Progression to permanent AF has been described by Hoogsteen et al. in 17% of individuals in an observational series.*

They conclude that, particularly in relatively recent LAF, limiting training may go a long way toward eliminating, or at least reducing, the severity of LAF in athletes. However, they point out, "these patients are very dependent on physical activity and it is difficult for them to follow this advice."

Mont, L, et al. Endurance sport practice as a risk factor for atrial fibrillation and atrial flutter. **Europace**, *Vol. 11, 2009, pp. 11-17*

Editor's comment: This latest article by Mont and colleagues add to the already substantial evidence that, while moderate exercise does the cardiovascular system a world of good, excessive endurance exercise, not only becomes an addiction, but also substantially increases the risk of developing lone AF. Fortunately, it would appear that it is possible to lessen the severity of the exercise-induced LAF by replacing the excessive training with some less intensive physical activity such as walking.

Lone afibbers really are unique!

KUOPIO, FINLAND. In one of our very first Conference Room Sessions (Proceeding #2, January 2003) we discussed the possible role of natriuretic peptides in lone atrial fibrillation (LAF). There are two natriuretic peptides of interest – ANP (atrial natriuretic peptide) and BNP (brain natriuretic peptide). ANP is a hormone formed by stretching of the walls of the atria. It helps regulate blood pressure and salt (Na) and water balance in body fluids. Its main action is to cause the excretion of

sodium and water via the kidneys and urine. Here is what we know about ANP:

- ANP levels are lower in people with LAF than in "normal" people.
- ANP levels decline with age and increased duration (years) of afib. This is probably due to the increase of fibrosis of the arterial wall over time.
- ANP is released during exercise. A stronger release predicts a better chance of staying in normal sinus rhythm (NSR).
- ANP levels are higher during an afib episode than during normal sinus rhythm.
- ANP levels are higher when laying on the right side (right lateral decubitus position).
- A higher ANP level predicts a quicker return to sinus rhythm.
- ANP blocks the calcium channels in cardiac myocytes.
- ANP suppresses the RAAS (renin-angiotensin-aldosterone system).

BNP is a hormone formed by stretching of the walls of the ventricles. Here is what we know about BNP:

- BNP causes the excretion of sodium and water via the kidneys and urine.
- BNP suppresses the renin-angiotensin-aldosterone system, lowers aldosterone level and inhibits the release of norepinephrine and other catecholamines.

One of the key observations in the above is that ANP levels are lower in people with LAF than in those without atrial fibrillation[1]. A group of Finnish researchers now report that high blood levels of ANP and BNP are potent markers of an increased risk of stroke and AF.

Their study involved 905 Finnish men between the ages of 46 and 65 years at baseline who had no history of heart failure, previous stroke, or AF. The average BMI of the men was 27.4 (slightly overweight), 28% were smokers, 21% had coronary heart disease, 33% hypertension, and 6% diabetes. The Finnish researchers measured blood plasma concentration of ANP and BNP (as N-terminal fragments) in all study participants and then followed them for an average of 9.6 years. During this time there were 46 cases of stroke (31 ischemic, 15 hemorrhagic) and 74 cases of new-onset AF giving a total stroke incidence of 0.5%/year, an ischemic stroke incidence of 0.36%/year, and a new-onset AF incidence of 0.85%/year. It is of interest that, at the end of the 10-year follow-up, the prevalence of AF among the men was 8%.

Analysis of the data collected revealed that men in the top 10% of ANP concentration (proA-type natriuretic peptide 455 pmol/L [mean]) had a 2.80-fold increased risk of ischemic stroke and a 3.2-fold increased risk of AF after adjusting for all confounding variables. Corresponding risk factors for men in the highest 90th percentile of BNP concentrations (mean of 133 pmol/L) were 2.12 and 3.71 respectively. The Finnish researchers conclude that elevated plasma levels of ANP and BNP (as measured by their N-terminal fragments of proANP and proBNP) could be used to predict the risk of stroke and AF.

Kurl, S, et al. Plasma N-terminal fragments of natriuretic peptides predict the risk of stroke and atrial fibrillation in men. **Heart**, *March 2009 [Epub ahead of print]*

Editor's comment: The finding that high ANP/BNP levels are associated with a 3-fold increase in the risk of ischemic stroke, combined with the observation that lone afibbers tend to have lower than normal ANP levels, may help explain why the risk of ischemic stroke is so low for lone afibbers.

[1] Mattioli, AV, et al. Clinical, echocardiographic, and hormonal factors influencing spontaneous conversion of recent-onset atrial fibrillation to sinus rhythm. American Journal of Cardiology, Vol. 86, August 1, 2000, pp. 351-52

Large cryoballoon catheter shows promise

HAMBURG, GERMANY. Paroxysmal (intermittent) atrial fibrillation (PAF) is the most common form of AF affecting about 80% of the afib population. The triggers for PAF are almost exclusively located within the pulmonary veins (PVs) so achieving electrical isolation of the PVs from the left atrium can often result in a complete cure of afib. A pulmonary vein isolation (PVI) is most frequently performed by using a radiofrequency (RF)-powered catheter to create a ring of lesions around each PV.

Since these rings are created point-by-point it is not uncommon for conduction gaps to occur following the initial procedure, thus necessitating a second ablation. Not surprisingly, a fair bit of research has gone into developing a ring-shaped catheter that would do the whole PV isolation with one or two applications. This would save time and may also result in better results for relatively inexperienced electrophysiologists.

A team of EPs from the Asklepios Clinic in Hamburg now report on their trial of a 28-mm diameter cryoballoon catheter (*Arctic Front*, Cryocath). This catheter is powered by cryoenergy and creates a ring-shaped lesion through the application of a balloon-shaped structure cooled to –80^{o}C with liquid nitrogen oxide. The Hamburg trial involved 27 afibbers (70% male) with paroxysmal AF of about 6 years standing (1 – 12 years). The average age of the patients was 56 years (47 – 65 years), average left atrial diameter was 4.2 mm (maximum 5.1 cm or 51 mm); all had highly symptomatic episodes with an average of 10 episodes a month and had not been helped by an average of 3 different antiarrhythmics. Eighty percent of the group were lone afibbers (no underlying heart disease), but 33% had hypertension.

All trial participants underwent a PVI procedure using the 28-mm cryoballoon and a Lasso catheter for mapping and checking of electrical potentials. No anatomical or other mapping was performed prior to the procedure. Overall, average procedure time was 3 hours and 40 minutes during which the balloon was present in the left atrium for 130 minutes and fluoroscopy was used for 50 minutes. Each PV was isolated with an average of two cryoballoon applications of 5 minutes duration each. Complete electrical isolation was achieved in 97 of 99 veins (98%). Recurrence rate (after a 3-month blanking period) was 30% one year following the procedure. However, when including the blanking period, only 52% of the 27 patients were still in sinus rhythm at the one-year end-point.

Unfortunately, it is not entirely clear how many of the afib-free patients were still on antiarrhythmics at the end of the trial. No pulmonary vein stenosis was observed, but 3 patients did experience phrenic nerve palsy, which eventually resolved on its own. It is noteworthy that the two electrophysiologists who performed the procedures had no prior experience with cryoballoon technology. NOTE: The two EPs did receive educational honoraria from Cryocath; however, the other 10 authors of the paper declared no conflict of interest.

Chun, KRJ, et al. The 'single big cryoballoon' technique for acute pulmonary vein isolation in patients with paroxysmal atrial fibrillation: a prospective observational single centre study. **European Heart Journal,** *Vol. 30, No. 6, March 2009, pp. 699-709*

Editor's comment: An overall single procedure success rate of 52% (with or without antiarrhythmics) is comparable to the 56% rate obtained at top-ranked RF ablation institutions and twice as good as the 26% average success rate observed for other than top-ranked RF institutions (2008 Ablation/Maze Survey). Thus, it would seem that the cryoballoon technique holds considerable promise for the treatment of PAF by less experienced EPs. It is quite possible that the success rate would improve substantially as operators gain more experience. Nevertheless, 12 months is a relatively short follow-up period and there are indicators that cryo-lesions may not be as durable as RF-lesions – so the jury is still out on this new, but highly promising technique.

Additional lesions required for persistent afibbers

BORDEAUX, FRANCE. In this article persistent atrial fibrillation (AF) is defined as AF lasting more than 7 days or lasting less than 7 days, but necessitating pharmacological or electrical cardioversion. Thus, permanent afib would appear to be included in this definition. It has long been known that persistent and permanent afib are far more difficult to cure with catheter ablation than is paroxysmal (intermittent) AF. While paroxysmal AF can often be cured by isolation of the pulmonary veins alone, the successful treatment of persistent/permanent AF requires the application of other lesions in the left atrium. It is now also clear that even a successful AF ablation is often followed by the development of atrial tachycardia (regular pulse rate in excess of 100 bpm).

Electrophysiologists at the Hopital Cardiologique du Haut Leveque recently concluded a clinical trial to determine the incidence of and the effect of additional lesions on post-procedure atrial tachycardia (AT) in a group of 180 patients with persistent AF. A comprehensive ablation procedure involving segmental pulmonary vein ablation (PVI),

electrogram-based ablation plus left atrial roof and/or mitral isthmus lines terminated AF in 154 patients, while the remaining 26 patients (14%) had to continue on antiarrhythmics. Among the 154 patients, 76% were men and they had suffered from persistent AF for an average of 5 years. Forty-five percent had structural heart disease and 14% had heart failure at the time of the procedure. Average left ventricular ejection fraction in the group was 57% and left atrial diameter (antero-posterior) ranged from 44 to 51 mm.

The 154 patients in which AF had been terminated were divided into two groups. Group A (55% of patients) consisted of those who had not required both roof and mitral lines in order to terminate the AF, while group B (45% of patients) consisted of those who had required both lines. Immediately following the procedure, 62% of group A developed AT as opposed to only 35% in group B. During a 28-month follow-up, 43% of patients developed AT recurrence and underwent re-ablation since this new rhythm disturbance was resistant to both antiarrhythmics and repeated cardioversion.

Ultimately, 82% of the 154 patients required both a mitral line and a roof line, 14% required the roof line only, 2% required the mitral line only, and 2% required no left atrium linear ablations. In group A, 76% required an additional linear lesion for AT either acutely or within the follow-up period. The corresponding number for group B was only 35%. The Bordeaux researchers conclude that, while it may be possible to terminate AF by catheter ablation without linear lesions, the majority of patients will ultimately require linear lesions for subsequently occurring macro re-entrant AT.

Knecht, S, et al. Left atrial linear lesions are required for successful treatment of persistent atrial fibrillation. **European Heart Journal,** *Vol. 29, 2008, pp. 2359-66*

Rostock, T and Willems, S. Rhythm-'a-line-ment' during catheter ablation of chronic atrial fibrillation. **European Heart Journal**, *Vol. 29, 2008, pp. 2321-22*

Editor's comment: Many afibbers with persistent/permanent afib have experienced in some cases very severe atrial tachycardia following an otherwise successful procedure for atrial fibrillation. The study by the Bordeaux researchers makes it clear that post-procedural AT is indeed very common and may ultimately require extensive linear ablation lines to overcome – one more reason for persistent/permanent afibbers to choose only the most experienced EP to perform the procedure.

Research Report

Digoxin: The Medicine From Hell?

Updated April 30, 2009

by Hans R. Larsen, MSc ChE

Despite incontrovertible evidence that digoxin (Lanoxin, digitalis, Digitek) should never be prescribed for **lone** atrial fibrillation some cardiologists still do so. Thus, I decided to update my 2002 article. You can find the updated article at http://www.afibbers.org/digoxin.pdf

Please feel free to share this article with anyone who might be interested, including your physician. The truth about the dangers of digoxin needs to be spread far and wide.

Digoxin, originally derived from the foxglove plant, has been in use for over 200 years as a heart medication. The drug raises the intracellular Ca^{2+} concentration resulting in an increase in the force of heart muscle contractions (positive inotropic effect) and a reduction in ventricular heart rate. From its original application digoxin has expanded into the treatment of atrial fibrillation and lone atrial fibrillation. Most medical textbooks still laud digoxin as an effective drug for heart failure, but does it actually work?

The Digitalis Investigation Group, a large team of American and Canadian researchers more than 10 years ago presented the findings of a large, randomized, double-blind, placebo-controlled trial of digoxin in the treatment of heart failure patients. The three-year trial involved over 7000 patients with heart failure (left ventricular ejection fraction less than 0.45). The patients were divided randomly into two equal-sized groups with one group receiving 0.250 mg of digoxin per day and the other group receiving a placebo; all patients in both groups

continued on ACE inhibitors and diuretics. The average follow-up time was 37 months. At the end of the trial 35% of the participants had died in each group. The death rate attributable to worsening heart failure was slightly less in the digoxin group, but the number of deaths from other cardiovascular events such as arrhythmias and strokes was higher. Patients on digoxin were less likely to be admitted to hospital for worsening heart failure (26.8 versus 34.7% for controls), but had higher admission rates for suspected digoxin toxicity (2.0 versus 0.9%)[1,2]. Digoxin is particularly dangerous for patients over the age of 60 years. In this age group the mortality associated with acute digoxin toxicity is almost 60%[3].

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

British researchers followed 484 heart failure patients for three years and found that the mortality among those taking digoxin was 38.9% as compared to only 21.3% among controls. The researchers conclude that the use of digoxin in heart failure patients is associated with an adverse prognosis and suggest that beta-blockers and spironolactone may be a better choice for ameliorating the symptoms of heart failure[4].

A team of American, Norwegian and Swedish researchers studied 7329 participants in the SPORTIF III and IV trials aimed at comparing the effectiveness of the anticoagulants warfarin (Coumadin) and ximelagatran in afib patients. About 53% of participants were on digoxin throughout the study. The researchers found a higher mortality (6.5%) in the digoxin group than in the group not using digoxin (4.1%). After adjusting for confounding variables, they conclude that digoxin users have a 53% (relative) higher mortality than do non-users. They suggest that in heart failure patients the adverse effects are counterbalanced by the positive inotropic effect, whereas in AF patients, who do not benefit from the inotropic effect, the adverse effects of digoxin dominate and lead to the 53% relative increase in mortality among users[5].

As if the inherent toxicity of digoxin was not enough to curtail its use, there is now also evidence that the drug, even at dosages normally considered safe, can cause visual problems, serious skin rashes, and may significantly aggravate asthma problems[6,7,8].

Of particular concern for women is the recent finding by a team of Danish and American researchers that digoxin increases the risk of breast cancer among postmenopausal women. Their study involved 5,565 women diagnosed with invasive breast cancer during the period 1991 to 2007 and 55,650 matched population controls. The researchers found that the use of digoxin for at least a year was associated with a 30% greater risk of being diagnosed with invasive breast cancer. The association did not change when adjusted for age, hormone replacement therapy, other drugs, medical history (reason for prescribing digoxin), and mammography exposure. The researchers conclude that digoxin treatment increases the risk of invasive breast cancer among postmenopausal women and that this risk increases with increasing duration of treatment[9].

Toxicity and Interactions

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

Researchers at the Health Care Department in Maryland found that in the period 1985 through 1991 over 200,000 of 3.3 million digitalis users were hospitalised because of digitalis intoxication. It is ironic that digitalis is often prescribed for people who suffer from atrial fibrillation and yet, the most common manifestation of digitalis intoxication is atrial fibrillation. Other symptoms of digitalis poisoning are nausea, vomiting, diarrhea, psychoses, and fatigue. Perhaps the most disturbing finding in the study is that in 73% of all cases the reason for prescribing the digitalis in the first place was unclear or weak. The researchers also point out that the high level of hospitalisation for adverse effects of digitalis is, to a large extent, due to inadequate monitoring of patients taking the drug. It is also of concern that for the period in which the researchers uncovered data for the 200,000 hospitalizations only 577 adverse events involving digitalis were reported directly to the FDA by doctors or hospitals[10].

Other researchers have noted that digoxin is often prescribed for seemingly no good reason. Dr. Wilbert Aronow of the Mount Sinai School of Medicine found that 19% of patients admitted to a nursing home had been prescribed digoxin. A thorough medical examination and evaluation concluded that 47% of these patients should not be taking digoxin at all. Dr. Aronow also noted that 18% of the patients receiving digoxin had been misdiagnosed as having congestive heart failure when, in fact, they were suffering from edema or dyspnea (laboured breathing). Digoxin therapy was safely discontinued in the 47% of the patients for whom it had been inappropriately prescribed.[11].

And if that is not enough, digoxin may also cause sinus bradycardia, heart block and ventricular arrhythmias, and interacts with a host of other medications among them amiodarone (Cordarone), flecainide (Tambocor), propafenone (Rythmol), tetracycline, calcium channel blockers, and the herbs Siberian ginseng and St. John's wort[12,13,14].

There is now also evidence that digoxin, when combined with the antidepressant paroxetine (Paxil), can result in severe digitalis toxicity. Japanese physicians recently reported a case of a 68-year-old woman who developed severe digoxin (digitalis) intoxication after starting on paroxetine (Paxil) for depression, insomnia, and difficulty concentrating. The patient had suffered from atrial fibrillation for 2 years and, during this time, had been treated with 0.25 mg digoxin and 1 mg warfarin daily. Two days after beginning on 20 mg/day of paroxetine she experienced nausea, vomiting, and dizziness. Delirium with visual hallucinations followed on day 4 and by day 8 she could no longer eat or walk. On day 9 the doctors suspected digitalis intoxication (serum digitalis concentration was 5.2 ng/mL compared to the normal range of 0.5-2.0 ng/mL). An ECG showed numerous PVCs and complete A-V block. On day 10 all medications were withdrawn resulting in the patient going into bradycardia as a rebound effect of discontinuing digoxin. On day 19 digoxin and warfarin (but not paroxetine) were restarted. The patient remained depressed, developed pneumonia, and died in hospital 3 months later. The physicians speculate that paroxetine and digoxin are metabolized via the same pathway and that the competition leads to digitalis intoxication[15].

Digoxin and Atrial Fibrillation

Almost 20 years ago, Dr. Rodney Falk MD, a leading electrophysiologist at Boston City Hospital made the following statement in an article entitled "Digoxin for Atrial Fibrillation: A Drug Whose Time has Gone?":[16]

> *Studies now suggest that in patients with atrial fibrillation, digoxin is a poor drug for controlling heart rate during exertion, has little or no effect in terminating the arrhythmia, and may occasionally aggravate paroxysmal atrial fibrillation.*

Nevertheless, digoxin is still routinely prescribed for patients with atrial fibrillation even though there is no evidence that it is beneficial and ample evidence that it may actually be harmful. Digoxin does not convert atrial fibrillation to sinus rhythm[17,18]. Its ability to slow the heart rate during an atrial fibrillation episode is doubtful[18] and there is no evidence that it prevents future episodes of paroxysmal atrial fibrillation[19,20]. Dr. Rodney Falk again sums it up, "*Digoxin is probably not of value for preventing tachycardia (rapid heart beat) at the onset of paroxysmal atrial fibrillation and its use as sole agent for this indication, although widespread, has no basis*"[20].

Not only is digoxin useless in the prevention and treatment of atrial fibrillation it can actually be detrimental. Dr. Philippe Coumel, MD head of the cardiology section of the Hopital Lariboisiere in Paris says, "*Not only are beta-blockers or digoxin not indicated in vagal atrial fibrillation, but they are definitely contraindicated as they tend to promote the arrhythmia and may block the action of conventional antiarrhythmic treatment*"[21]. Dr. Coumel's statement has been endorsed by the American Heart Association[22].

Researchers at the University of Michigan Medical Center go even further in their condemnation of digoxin. Their conclusion from a recent clinical trial, "The results of the present study suggest that digoxin may facilitate or promote early recurrences of atrial fibrillation after conversion to sinus rhythm not only in patients with vagotonic (vagal) atrial fibrillation, but also among the general population of patients with atrial fibrillation"[23]. It is now also clear that digoxin may not only prolong the duration of episodes, but may actually convert the paroxysmal (intermittent) form to chronic AF[24].

Digoxin also interferes with cardioversion. The 2006 Guideline for the Management of Atrial Fibrillation clearly states, "Digoxin and sotalol may be harmful when used for pharmacological cardioversion of AF and are not recommended"[25].

Digoxin is also a problem for persistent afibbers undergoing electrical cardioversion. Researchers at Lund University Hospital in Sweden found that being on digoxin at time of cardioversion was associated with a 2.3-fold increase in risk of relapse into afib. They also noticed that patients on digoxin had significantly longer episodes than did afibbers not on digoxin[26].

Perhaps most disturbing is the recent observation made by Swedish researchers that, although digoxin has been routinely prescribed for AF patients for close to 100 years, its long-term safety has never been evaluated in this patient population. Their recent study involved 21,459 atrial fibrillation patients admitted to a coronary care unit in Sweden during the period 1995 to 2003. The overall mortality in this group was 9.8%/year, but the annual death rate was 42% higher among digoxin users than among those who had not been prescribed digoxin.

All mortality rates were adjusted for about 60 possible confounding variables (other possible risk factors for death). Of particular interest to lone afibbers is the finding that the detrimental effects of digoxin were far worse for relatively healthy patients than for those with multiple risk factors. Thus, AF patients with AF and the least number of other risk factors were more than twice as likely to die within a year after leaving hospital if they had been prescribed digoxin.

The researchers conclude that digoxin is an independent risk factor for death among AF patients placed on long-term therapy with the drug. They also re-emphasize that there is no evidence that digoxin is helpful in speeding up conversion to normal sinus rhythm, or in preventing recurrence of AF episodes[27].

Finally, our own LAF Survey V confirms the inappropriateness of prescribing digoxin for lone afibbers. Twenty-two (12 vagal, 1 adrenergic, 9 mixed) afibbers had tried digoxin. Only 1 mixed afibber had found it useful in keeping heart rate under control. The remaining 21 (95%) had found no benefits from taking the drug. Seventeen (77%) of all users reported side effects with the most common being palpitations and atrial fibrillation (32%) and fatigue (23%). The most common dosage was 0.25 mg daily[28].

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

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