THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation!

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Welcome to our 2009 summer issue! Twenty-five years ago Dr. Philippe Coumel of the Lariboisiere Hospital in Paris postulated that lone atrial fibrillation only occurs when the following three conditions are met:

1. *The heart tissue (myocardium) is abnormally sensitive and capable of being triggered into and sustaining an afib episode.*
2. *The autonomic nervous system is out of balance (overly vagal or overly adrenergic).*
3. *A trigger or precipitating cause capable of initiating an afib episode is present.*

While a fair bit of research has been done in regard to conditions 2 and 3, so far little attention has been devoted to determine why the myocardium is "abnormally sensitive". Dr. Prash Sanders and colleagues at the Royal Adelaide Hospital have now stepped in to fill this very important gap in our knowledge regarding the mechanism underlying lone atrial fibrillation. Read more about this very important work in this issue.

Also in this issue, we report that left atrial function is somewhat impaired after a PVI, that afibbers with hypertension, but no heart disease, may wish to avoid beta-blockers, that N-acetylcysteine prevents contrast-induced kidney damage, that magnesium improves cardioversion results, and that Professor Michel Haissaguerre and colleagues in Bordeaux now report that experiencing atrial tachycardia following an ablation is a good indication that the ablation is likely to be successful in the long term.

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 and an enjoyable and safe summer,

Hans

Highlights

Stroke risk and mortality

COPENHAGEN, DENMARK. There are two major types of stroke – ischemic stroke is caused by an obstruction in a small artery resulting in stoppage of the blood supply to an area of the brain (infarction). A hemorrhagic stroke does not involve an obstruction but rather a rupture of a blood vessel, which results in interrupting the blood supply to the affected area of the brain. Ischemic stroke can be further divided into two types – thrombotic and embolic. Both involve the obstruction and subsequent stoppage of the blood supply to an area of the brain (infarction). However, the mechanism by which the obstruction occurs differs.

A thrombotic stroke involves the formation of atherosclerotic plaque and subsequent narrowing and clot (thrombus) formation at the point of obstruction. In an embolic stroke, on the other hand, the obstruction is caused by the lodging of an embolus (blood clot or atherosclerotic plaque) formed in the heart or in an artery outside the brain. Cardiogenic emboli (blood clots originating in the

heart) can form on heart valves, particularly prosthetic ones, or as a result of mitral stenosis. Cardiogenic emboli can also originate from the walls of the heart as a result of a heart attack (myocardial infarction), atrial fibrillation or congestive heart failure or from a benign atrial tumour (myxoma).

A group of Danish medical doctors and statisticians have just completed a major study to determine the risk factors, severity and incidence of ischemic and hemorrhagic stroke in Denmark. Their study involved almost 40,000 patients who had suffered a stroke in the period from March 2001 to February 2007. Of these patients 25,123 had complete data including CT or MRI scans, admission stroke severity as measured by the Scandinavian Stroke Scale (SSS), risk factors, and ultimate outcome (survival or death). The highlights of the study are:

- Ten percent of the strokes recorded were hemorrhagic and these tended to be considerably more severe than the ischemic strokes.

- The risk of dying from a hemorrhagic stroke was 13% during the first 7 days, 20% during the 30 days following the stroke, and 25% during the 90 days following. Corresponding mortality rates for ischemic strokes were 1.8%, 4.8%, and 11%. All told, 49% of hemorrhagic stroke victims died during the follow-up as compared to 26% in the ischemic stroke group.

- The major risk factors favoring ischemic stroke over hemorrhagic stroke were intermittent arterial claudication, a previous stroke or heart attack, diabetes, and atrial fibrillation.

- The major risk factors favoring hemorrhagic stroke were smoking and heavy alcohol consumption.

- There was no difference in gender, age and prevalence of hypertension between patients with ischemic stroke and those with hemorrhagic stroke.

The researchers conclude that hemorrhagic strokes are generally more severe and have a poorer outcome than do ischemic strokes.
Andersen, KK, et al. Hemorrhagic and ischemic strokes compared: stroke severity, mortality, and risk factors. **Stroke**, *Vol. 40, June 2009, pp. 2068-72*

Editor's comment: It is unfortunate that the researchers did not include an evaluation of the relative risk of ischemic versus hemorrhagic stroke in patients taking warfarin or aspirin. Both drugs are acknowledged as important risk factors for hemorrhagic stroke. Nevertheless, it is of considerable interest to establish that the risk factors favoring one type of stroke over the other are different. In considering the above results, it should be kept in mind that AF on its own is not a risk factor for ischemic stroke. It only becomes one when accompanied by other risk factors such as hypertension and heart disease.

C-reactive protein and ablation success

PARIS, FRANCE. There is ample evidence that catheter ablation (PVI) for atrial fibrillation (AF) is accompanied by a state of systemic inflammation. What is not known is whether the extent of the post-procedure inflammation, as measured by C-reactive protein (CRP) level, is helpful in predicting the short- and long-term success of the procedure.

A team of French EPs investigated this question in a recent study of 125 afibbers who had their first AF ablation between July 2005 and April 2007. Most of the patients (78%) were male, 21% had underlying heart disease, 14% had hypertension, and 52% had the paroxysmal variety of AF. All underwent a standard segmental pulmonary vein isolation procedure (Haissaguerre protocol) and had their blood level of CRP measured prior to the procedure and at 1, 2 and 3 days following the procedure. The CRP level peaked on day 2 with an average level of 40 mg/L (4 mg/dL).

The researchers observed a clear correlation between the day 2 CRP level and the incidence of early arrhythmia occurrence. The average CRP level on day 2 for patients who experienced an arrhythmia (AF, tachycardia or incessant PACs) during the first month following the procedure was significantly lower (32 mg/L) than for those who did not experience early recurrence (49 mg/L). However, there was no significant difference in CRP levels between patients who did or did not experience arrhythmia recurrence in the 13-month follow-up period beyond the first month. The researchers speculate that location or depth of the

radiofrequency (RF) lesions could influence the systemic inflammation response.

Lellouche, N, et al. Usefulness of C-reactive protein in predicting early and late recurrences after atrial fibrillation ablation. **Europace**, *Vol. 11, May 2009, pp. 662-64*

Post-ablation left atrial function

SAO PAULO, BRAZIL. A catheter ablation for atrial fibrillation 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. The most important parameters in evaluating the pumping action of the left atrium are the left atrial emptying fraction (EF) and the flow velocity (FV) through the mitral valve (the valve between the left atrium and the left ventricle). The EF is defined as the maximal minus the minimal left atrial volume divided by the maximal volume. The FV is obtained from echocardiographic measurements.

Electrophysiologists at the University of Sao Paulo now report that left atrial function is indeed impaired immediately following an ablation, but then improves over time. Their study involved a control group of 28 age- and gender-matched healthy individuals without afib and 28 paroxysmal afibbers. All the AF patients had normal left ventricular ejection fractions and no significant structural heart disease. However, 39% did have hypertension and 18% had undergone a previous ablation. At baseline (prior to ablation) members of the control group had a significantly shorter left atrial diameter (average 36 mm vs. 41 mm), a significantly higher average EF (53% vs. 47%), and a greater FV (average 10.2 cm/s vs. 8.2 cm/s) than members of the afib group.

The paroxysmal afibbers underwent a standard pulmonary vein isolation (PVI) procedure and then had their EF and FV measured 24 hours and an average of 8 months following the procedure (minimum 6 months post-procedure). Sixty-one percent of ablatees were in normal sinus rhythm at both the 24-hour and 8-month evaluations. The researchers found that the average EF in the PVI group decreased from the baseline 47% to 40% 24 hours after the ablation. However, at the 8-month check-up it had recovered to 43%. Similarly, the FV decreased from an average 8.2 cm/s at baseline to 6.9 cm/s at the 24-hour mark, but then increased to 7.7 cm/s over the following 8 months.

The researchers conclude that a PVI causes a significant drop in left atrium performance immediately after the procedure, but that the performance improves with time. They did not observe any decrease in left atrial diameter or volume after the procedure, but speculate that this could, at least partially, be due to the fact that 39% of the group were still experiencing afib episodes following their ablation.

Rodrigues, ACT, et al. Left atrial function after ablation for paroxysmal atrial fibrillation. **American Journal of Cardiology**, *Vol. 103, 2009, pp. 395-98*

Hypertension and beta-blockers

NEW YORK, NY. An elevated resting heart rate is an independent risk factor for cardiovascular disease and associated mortality. Beta-blockers (propranolol, atenolol, metoprolol) are effective in lowering heart rate and have been found to reduce mortality among patients with heart failure and angina. There is also evidence that beta-blocker therapy reduces the severity and mortality of heart attacks (myocardial infarctions). This has led to the assumption that the slower the heart rate the better and has resulted in beta-blockers being routinely prescribed for patients with elevated blood pressure (hypertension) even though there is no clinical evidence that reducing heart rate is of benefit in these patients.

Dr. Franz Messerli and colleagues at Columbia University of Physicians and Surgeons now report that prescribing beta-blockers for patients with hypertension is precisely the wrong thing to do. Their meta-analysis encompassed 9 randomized, controlled clinical trials evaluating the effects of beta-blockers among hypertensives. A total of 34,096 patients were treated with beta-blockers, 30,139 were treated with other anti-hypertensive

agents (diuretics, ACE inhibitors or calcium channel blockers) and 3,987 were given a placebo.

All patients were followed for an average of 3.5 years (minimum 1 year) by which time their average systolic blood pressure had decreased by about 13% in both the beta-blocker group and the comparison group. In addition, average resting heart rate had decreased by 12% in the beta-blocker group, while a statistically non-significant decrease of 1% was observed in the comparison group (other anti-hypertensive agents). Surprisingly, the New York researchers observed an inverse relationship between the extent of heart rate reduction and cardiovascular mortality during the studies. In other words, the more effective the beta-blockers were at reducing heart rate, the greater the mortality. Similar correlations were observed for nonfatal myocardial infarction (MI), heart failure and stroke. In all cases, the incidence of these conditions increased as the heart rate was lowered using beta-blocker therapy.

The researchers conclude that, "In contrast to patients with MI and heart failure, beta-blocker-associated reduction in heart rate increased the risk of cardiovascular events and death for hypertensive patients." They speculate that the beta-blocker induced heart rate reduction increases central aortic pressure or pulse pressure and that this is responsible for the adverse effects observed in patients with hypertension.

In an accompanying editorial, Dr. Normal Kaplan of the University of Texas points out that beta-blockers have numerous other adverse effects including precipitation of diabetes, weight gain, and a decrease in exercise endurance. Despite this, atenolol was the 4th most prescribed drug in the US in 2005 with 44 million prescriptions a year.

Bangalore, S, et al. Relation of beta-blocker-induced heart rate lowering and cardioprotection in hypertension. **Journal of the American College of Cardiology**, Vol. 52, October 28, 2008, pp. 1482-89

Kaplan, NM. Beta-blockers in hypertension: Adding insult to injury. **Journal of the American College of Cardiology**, *Vol. 52, October 28, 2008, pp. 1490-91*

Editor's comment: It should be kept in mind that 78% of the participants in the clinical trials were prescribed atenolol (Tenormin), so it is not entirely clear whether beta-blockers as such, or atenolol in particular, are responsible for the adverse effects. It is quite possible that one of the newer vasodilating beta-blockers such as nebivolol (Bystolic) would not have the same detrimental effects as atenolol since it does not increase the central aortic pressure. Nevertheless, with the evidence at hand, it would seem that lone afibbers with hypertension would be far better of taking an ACE inhibitor, calcium channel blocker, or potassium-sparing diuretic rather than a beta-blocker for reducing their blood pressure.

Warfarin not always required following ablation

MURRAY, UTAH. Current guidelines for stroke prevention after catheter ablation for atrial fibrillation (AF) call for anticoagulation with warfarin (Coumadin) for at least 2 months following the procedure. Electrophysiologists at the Intermountain Medical Center now report that warfarin therapy may not be necessary among afibbers with no or only one stroke risk factor [hypertension, diabetes, heart failure, age over 75 years, and a history of prior stroke or transient ischemic attack (TIA)].

Their study involved 690 AF patients who underwent a total of 934 ablation procedures (repeat rate of 35%) at the Center during the period 2005 to 2008. The average age of the study participants was 65 years and 52% had paroxysmal, 30% persistent, and 18% permanent AF. The procedure protocol was quite extensive and involved not only a standard PVI, but also the placing of left atrial ablation lines in 69% of the patients and mapping and ablation of complex fractionated electrograms and sites of frequent atrial ectopy. Ablation was carried out with an open-tip irrigated catheter using ICE (intracardiac echocardiography) guidance. Patients were followed for one year through clinic visits and telephone contact. At the end of the follow-up period 71.6% of ablatees were in normal sinus rhythm without the use of antiarrhythmic drugs.

Of the 630 patients, 20% were discharged on 325 mg/day of aspirin, while the remaining 80% were discharged on warfarin (INR to be controlled between 2.0 and 3.0). The aspirin group consisted of younger afibbers (average age of 60 years) with, at the most, one risk factor for ischemic stroke (41% had 0 risk factors, and 59% had 1 risk factor). Only

14% had structural heart disease so the aspirin group consisted mainly of lone afibbers, although 55% did have hypertension. In contrast, the patients in the warfarin group were older (average age of 66 years) and generally unhealthier. Only 14% of the group had no risk factors for stroke, 32% had 1 risk factor, and the remaining 52% had 2 or more risk factors. Warfarin group patients were also more likely to have persistent or permanent afib than were those in the aspirin group (55% vs. 22%).

During the year following the ablation procedure there were no deaths, strokes, TIAs or other cerebrovascular events in the aspirin group. There were 5 deaths and 4 strokes in the warfarin group. The stroke victims had 2, 3 or 4 risk factors for stroke. Two of the deaths in this group were due to major gastrointestinal and intracranial bleeding (hemorrhagic stroke). It is of interest to note that substantially more patients in the aspirin group, which consisted mainly of lone afibbers, were free of afib at the end of the follow-up than was the case for the warfarin group. In the aspirin group, 92% of paroxysmal afibbers were free of afib as compared to only 66% in the warfarin group. Corresponding percentages for persistent/permanent afibbers were 90% and 70%.

The Intermountain EPs conclude that AF patients with none or, at the most, one risk factor for ischemic stroke do not need to be anticoagulated with warfarin following a catheter ablation for AF provided the protocol used involves the use of ICE guidance and an open-tip, irrigated catheter which is less likely to result in clot formation during the procedure.

Bunch, TJ, et al. Warfarin is not needed in low-risk patients following atrial fibrillation ablation procedures. **Journal of Cardiovascular Electrophysiology** [Epub ahead of print]

Editor's comment: As all who have experienced it, being on warfarin is a real nuisance and dangerous as well if inadequately monitored. It is therefore of considerable interest that lone afibbers with none or, at most, one risk factor for ischemic stroke do not need to be on warfarin after their ablation procedure.

Atrial substrate in lone afibbers

ADELAIDE, AUSTRALIA. Twenty-five years ago Dr. Philippe Coumel of the Lariboisiere Hospital in Paris postulated that lone atrial fibrillation only occurs when the following three conditions are met:

1. The heart tissue (myocardium) is abnormally sensitive and capable of being triggered into and sustaining an afib episode.
2. The autonomic nervous system is out of balance (overly vagal or overly adrenergic).
3. A trigger or precipitating cause capable of initiating an afib episode is present.

While a fair bit of research has been done in regard to conditions 2 and 3, so far little attention has been devoted to determine why the myocardium is "abnormally sensitive".

Dr. Prash Sanders and colleagues at the Royal Adelaide Hospital have now stepped in to fill this very important gap in our knowledge regarding the mechanism underlying lone atrial fibrillation. Before getting into details of their study it is, however, necessary to ensure that the reader has a basic understanding of the parameters governing normal as well as abnormal heart rhythms (arrhythmias).

Heart Rhythm 101

The membrane (sarcolemma) of a resting heart cell (myocyte) is polarized – that is, the inside (intracellular space) of the cell (cytoplasm) is negatively charged in respect to the outside environment (extracellular space). Responding to an impulse from the sinoatrial (SA) node (the heart's natural pacemaker controlled by the autonomic nervous system) the myocytes depolarize resulting in contraction of the heart muscle. The *depolarization* is caused by a rapid influx of positive sodium (Na^+) ions followed by a slower influx of calcium ions (Ca^{++}). During depolarization the outward leakage of potassium ions (K^+) is restricted. Atrial depolarization shows up as a P wave on an electrocardiogram (ECG) while ventricular depolarization is identified as the QRS complex – that is, the time period on the ECG during which the ventricles depolarize (contract). The P wave is absent during atrial fibrillation. The time interval between the start of the P wave and the beginning of the QRS complex is a vulnerable period for afib initiation.

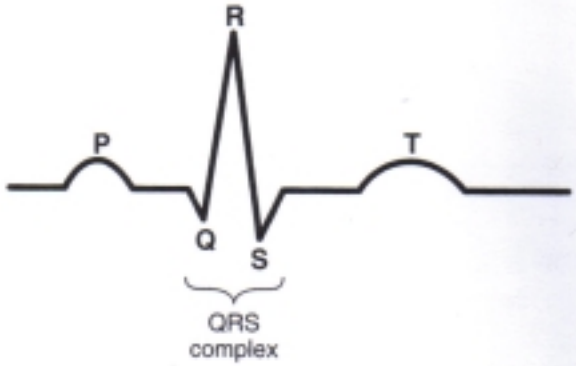
Depolarization is followed by *repolarization* (recovery). During this phase, an outflow of K^+ ions is followed by a period during which the intracellular concentrations of K^+ and Na^+ in the myocytes are restored to their resting potential through the action of Na^+/K^+ ATPase pumps "powered" by magnesium. Magnesium ions (Mg^{++}) also play an important role during this phase by slowing down the outward (from intracellular space to extracellular space) flow of potassium ions. At the risk of oversimplification, one could say that while Na^+ and Ca^{++} are "excitatory" ions K^+ and Mg^{++} ions are "calming". Thus it is not surprising that a deficiency of K^+ and Mg^{++} facilitate atrial fibrillation. Repolarization is identified on the ECG as the time period from the end of ventricular depolarization to the peak of the T wave (ST segment).

The *atrioventricular (AV) node* is a specialized conglomeration of myocytes that acts as the speed controller for ventricular contractions (depolarization) just as the SA node does for atrial contractions. Normally, the AV node receives its "instructions" directly from the SA node through a well-defined "wiring circuit"; however, during atrial fibrillation the AV node is bombarded by impulses from rogue atrial cells which, if they are not filtered out by the AV node will cause the rapid, irregular ventricular contractions characteristic of atrial fibrillation.

The period from the start of the QRS complex to the peak of the T wave is of particular interest when it comes to atrial fibrillation. During this period (the *effective refractory period or ERP*) myocyte depolarization cannot be triggered by stimulus originating from rogue atrial cells thus preventing afib from being initiated. However, atrial fibrillation can be triggered during the last half of the T wave (*relative refractory period or RRP*) making it highly desirable that the ERP is as long as possible and the RRP as short as possible. Several medications aim to exploit this fact by acting to extend the ERP so that the RRP (the vulnerable period) becomes as short as possible. This is particularly important in the case of the AV node as during the ERP the node cannot be stimulated and thus in essence filters out the erratic atrial impulses.

The speed with which an electrical impulse moves across the atrium (normally directly from the SA node to the AV node) is called the *conduction velocity* and is a measure of the effectiveness of cell-to-cell depolarization. It is measured in millimeter/millisecond (mm/ms) or in meter/second (m/s). Sympathetic (adrenergic) stimulation increases conduction velocity while parasympathetic (vagal) stimulation reduces it. Slow conduction is associated with the presence of *complex fractionated atrial electrograms* (CFAEs) defined as electrograms (direct measurements of electrical activity inside the atrium) with a cycle length less than or equal to 120 ms or shorter than in the coronary sinus or that are fractionated or display continuous electrical activity. CFAEs are believed to be associated with fibrosis and serve as targets in some ablation procedures for atrial fibrillation.

Electrocardiogram (ECG) of Normal Heartbeat



P-wave: Atrial depolarization (contraction)

QRS Complex: Ventricular depolarization (contraction)

T-wave: Ventricular repolarization (recovery)

ST Segment: From end of QRS complex to peak of T-wave (Repolarization)

ERP: From beginning of QRS complex to peak of T-wave

RRP: Last half of T-wave

The Adelaide team performed an exhaustive electrophysiological study on 25 paroxysmal lone afibbers (average age 53 years, 80% male, average duration of afib 5 years, longest episode 3 days) who had been in sinus rhythm for the previous 7 days and compared the results to those obtained in a group (reference group) of afib-free patients who were undergoing ablation for atrioventricular tachycardia (left-sided accessory pathway). Using two 10-pole and two 20-pole catheters to carry out measurement in both atria, the team observed the following major differences between the afib group and the reference group:

- Members of the afib group had a significantly larger left atrium (average parasternal diameter of 41 mm) than did those of the reference group (34 mm). The average right atrium volume was 94 mL in the afib group (69 mL in reference group) and the left atrial volume was 99 mL versus 77 mL in the reference group.
- The ERP was measured at 10 different sites at pacing rates of 100 bpm (600 ms/cycle) and 135 bpm (450 ms/cycle). The researchers found that the ERPs at all sites were longer in duration when paced at 100 bpm than when paced at 135 bpm. Generally, ERPs were also longer in the afib group than in the reference group, which is somewhat surprising since remodeling in AF patients is known to shorten ERP.
- P wave duration was significantly longer in the afib group than in the reference group (128 ms vs. 95 ms).
- Patients with afib had a significantly greater number of points with double potentials or fractionated signals than did reference patients (27% vs. 8%)
- AF patients had impaired sinus node function as indicated by a substantially

longer corrected sinus node recovery time (at 100 bpm pacing) than found in the reference group (average 265 ms vs. 185 ms).

- The mean voltage measured between poles in the catheters was significantly less in the afib group than in the reference group. In the right atrium 1.7 mV vs. 2.9 mV and in the left atrium 1.7 mV vs. 3.3 mV - a decrease of 41% and 48% respectively.

- Afibbers had a significantly slower mean conduction velocity during sinus rhythm than did the reference group. In the right atrium the conduction velocity was 1.3 mm/ms in the afib group versus 2.1 mm/ms in the reference group. Corresponding numbers for the left atrium were 1.2 mm/ms vs. 2.2 mm/ms.

The Australian researchers conclude that lone, paroxysmal afibbers have an abnormal atrial substrate and that this abnormality is what promotes progression of AF. They also reach the somewhat discouraging conclusion that "sinus rhythm does not beget sinus rhythm". Other observations made by the team include:

- Patients with recent AF have been shown to have shorter ERP than control groups, as well as sinus dysfunction and conduction delay.

- The predominant contributors to the abnormal substrate underlying AF are the structural and associated conduction abnormalities rather than changes in refractoriness. Future strategies to treat AF should focus on atrial myocardial structure and conduction.

- Pulmonary vein isolation is highly successful in eliminating afib; however, data on long-term outcome is very limited. The findings of the study raises the possibility of continuing modification of the atrial substrate perhaps eventually leading to renewed afib despite early procedural success.

In an accompanying editorial Dr. Maurits Allessie from the University of Maastricht suggests that the results of an electrophysiological study such as carried out by the Australian group, with particular emphasis on atrial enlargement and conduction abnormalities, may be useful in predicting the risk of paroxysmal afib progressing to the persistent or permanent variety.

Stiles, MK, et al. Paroxysmal lone atrial fibrillation is associated with abnormal atrial substrate. **Journal of the American College of Cardiology**, *Vol. 53, April 7, 2009, pp. 1182-91*

Allessie, M. The "second factor": a first step toward diagnosing the substrate of atrial fibrillation? **Journal of the American College of Cardiology**, *Vol. 53, April 7, 2009, pp. 1192-93*

Editor's comment: The study by Prash Sanders and colleagues will, no doubt, be cited as a landmark study in future years. While it has long been assumed that lone afibbers have an abnormal atrial substrate, this is the first time that the abnormalities have been clearly defined. We now know that the following features are characteristic of the atria in lone, paroxysmal afibbers:

1. Distinct signs of inflammation and fibrosis[1];
2. Larger than normal volume of both atria and a longer left atrial parasternal diameter;
3. Longer than normal effective refractory period (ERP). NOTE: This finding is likely to be controversial;
4. Longer P wave duration;
5. Greater number of complex fractionated electrograms (points of abnormal electrical activity and slowed conduction);
6. Slower conduction velocity;
7. Impaired sinus node function;
8. Lower voltages in both atria.

While the approach of the Adelaide team and the majority of researchers in the field will, no doubt, be to develop pharmaceutical drugs that target one or more of these abnormalities, there is an alternative – to determine what causes or caused the abnormalities in the first place and then devise strategies to deal with these causes directly. It is likely that magnesium and, to some extent, potassium deficiencies will rank high as causal factors in lone atrial fibrillation, especially in view of the recent finding by Sachin Shah and his team at Hartford Hospital that 90% of lone afibbers are deficient in intracellular magnesium although their serum levels are in the normal range[2].

For a detailed discussion of the importance of magnesium and potassium in lone AF please see Dr. Patrick Chambers' excellent article "Magnesium and Potassium in LAF" at http://www.afibbers.org/conference/PCMagnesium.pdf

[1] Frustaci, A, et al. Histological substrate of atrial biopsies in patients with lone atrial fibrillation. *Circulation*, Vol. 96, August 19, 1997, pp. 1180-84

[2] Shah, SA, et al. The impact of magnesium sulfate on serum magnesium concentrations and intracellular electrolyte concentrations among patients undergoing radio frequency catheter ablation. *Connecticut Medicine*, Vol. 72, May 2008, pp. 261-65

N-acetylcysteine prevents contrast-induced nephropathy

SEOUL, KOREA. Contrast-induced nephropathy (CIN) is a leading cause of hospital-acquired renal failure and associated mortality. Contrast agents (x-ray dyes) are used routinely to "amplify" the x-ray image of the heart and arteries during such procedures as coronary angiography and catheter ablation. Unfortunately, commonly used contrast agents are hard on the kidneys and their use can result in kidney failure in patients who already have impaired kidney function. Several studies have shown that the natural antioxidants N-acetylcysteine (NAC) and ascorbic acid (vitamin C) can reduce the risk of kidney failure in susceptible patients if administered in relatively large doses prior to and subsequent to the procedure.

A group of researchers from the Seoul National University Hospital recently carried out a controlled clinical trial to determine which of the two antioxidants, NAC or ascorbic acid (AA), is the most effective in preventing CIN. Their trial included 212 patients with renal impairment (basal creatinine clearance at or below 60 mL/min and/or serum creatinine level (SCr) of 1.1 mL/dL (100 mmol/L) or higher. The patients were all on statin drugs for elevated cholesterol levels. Over 60% had hypertension, about 40% had diabetes, and almost 50% were current smokers – not a healthy bunch!

The study participants were all scheduled to undergo coronary angiography with the use of the iodine-containing contrast agent iodixanol. They were randomized to receive either 1200 mg of NAC (orally) every 12 hours starting the evening prior to the procedure followed by another two 1200 mg doses (12 hours apart) starting the evening after the procedure, or to receive 3 grams and 2 grams of AA prior to the procedure and 2 grams twice following the procedure with all AA doses being given 12 hours apart. Serum creatinine levels were measured in the morning on the day prior to the angiography procedure and in the morning of days 1 and 2 following.

The researchers found that SCr levels tended to peak on day 2 at which time the average SCr level in the NAC group had decreased by 0.03 mg/dL (2.7 mmol/L) over baseline, while it had increased by 0.04 mg/dL (3.3 mmol/L) in the AA group. The protective effect of NAC was particularly impressive in a subgroup of patients with diabetes. Here NAC decreased SCr by an average of 0.05 mg/dL (4.4 mmol/L) over baseline, while members of the AA group saw an average increase in SCr of 0.09 mg/dL (8 mmol/L).

The incidence of CIN was 1.2% in the NAC group versus 4.4% in the AA group. Again, the protective effect of NAC was particularly impressive among diabetics where 0% experienced CIN as compared to 12.5% who experienced CIN (kidney damage) in the AA group. The Korean researchers conclude that NAC is more effective than ascorbic acid in preventing contrast-induced nephropathy, especially in patients with diabetes.

Jo, SH, et al. N-acetylcysteine versus ascorbic acid for preventing contrast-induced nephropathy in patients with renal insufficiency undergoing coronary angiography. **American Heart Journal**, *Vol. 157, March 2009, pp. 576-83*

Editor's comment: The finding that n-acetylcysteine (NAC) is highly effective in preventing further kidney damage in patients with already impaired kidney function if highly important in its own right. However, the cut-off point of 1.1 mg/dL (100 mmol/L) above which kidney function is considered to be impaired is arbitrary. There is no reason to believe that if NAC protects a person with a SCr of 1.2 mg/dL (106 mmol/L) from kidney damage that it would not also protect a person with an SCr level of 0.9 mg/dL (80 mmol/L) or even lower. Thus, it would seem prudent for all afibbers scheduled to undergo a catheter ablation to ensure that they, along with the appropriate pre-procedure hydration regimen, receive two 1200 mg doses of NAC prior to the procedure (12 hours apart) followed by two 1200 mg doses following the procedure.

Magnesium improves cardioversion results

HARTFORD, CONNECTICUT. A group of Austrian researchers recently reported that pre-injection of magnesium sulfate considerably improves the efficacy of pharmaceutical conversion with ibutilide (Corvert). In a group of 65 patients with typical right atrial flutter the conversion effectiveness with magnesium was 85% as compared to 59% with placebo.

Now physicians at the Hartford Hospital report that pre-injecting magnesium sulfate also improves the cardioversion efficacy of dofetilide (Tikosyn) when used in patients with atrial fibrillation. Their clinical trial involved 150 patients with AF and 10 with atrial flutter. The average age was 67 years and the majority of participants had pretty severe health problems including heart failure (38%) and hypertension (54%), and the average left ventricular ejection fraction in the group was a very low 36%. All patients had normal serum levels of magnesium at baseline – average value of 2.1 mg/dL vs. normal range of 1.7 - 2.6 mg/dL. The patients were evaluated in two groups – one group of 100 patients received the standard dofetilide protocol (6 doses over 3 days), while the remaining 50 patients also received intravenous magnesium sulfate (average of 3 grams) on the first day of dofetilide administration and another 3 grams (average) over the next 2 days. This corresponds to a total average intake of elemental magnesium of 1200 mg over the 3-day hospital stay.

The overall conversion rate was 41.9%; however, the rate of successful conversion was substantially higher in the magnesium group (50%) than in the no magnesium group (38.2%). The increase in cardioversion efficiency was only statistically significant in the afib group – here patients who had received magnesium + dofetilide were more than twice as likely to be successfully converted than were those who received dofetilide only. The Hartford group speculates that the beneficial effects associated with magnesium is due to its role in maintaining high intracellular potassium concentrations and in its ability to regulate intracellular calcium concentration or directly oppose the actions of calcium.

Steinwender, C, et al. Pre-injection of magnesium sulfate enhances the efficacy of ibutilide for the conversion of typical but no of atypical persistent atrial flutter. **International Journal of Cardiology**, *2009 [Epub ahead of print]*

Coleman, CI, et al. Intravenous magnesium sulfate enhances the ability of dofetilide to successfully cardiovert atrial fibrillation or flutter. **Europace**, *April 6, 2009 [Epub ahead of print]*

Editor's comment: This study again shows that patients can have normal serum levels of magnesium and yet receive substantial benefits from a magnesium injection. It would certainly seem advisable for patients contemplating cardioversion with dofetilide (Tikosyn) to ask for a pre-procedure magnesium sulfate injection.

TEE and cardioversion

MILAN, ITALY. Electrical cardioversion in the presence of a blood clot (thrombus) in the left atrium is dangerous in that the electric shock may dislodge the clot and send it on its way to the brain where it may cause an ischemic stroke. Thus, cardioversion is usually not attempted unless the patient has been in afib for less than 48 hours or has been treated with warfarin for at least 3 weeks prior to the attempted cardioversion. As an alternative to waiting 3 weeks patients may undergo a TEE (transesophageal echocardiogram) and if this shows no evidence of thrombi the cardioversion may safely proceed. A TEE cannot only detect thrombi, but can also detect the presence of so-called spontaneous echocontrast (SEC) which is considered a forerunner for thrombi. SEC is seen as a swirling pattern (fog) on the TEE and the denser the pattern the more likely it is that a clot will eventually develop. The most dense pattern, presumably just prior to clot formation, is called "sludge".

A group of Italian researchers recently conducted a study to determine the effectiveness of various anticoagulation protocols in preventing SEC and also to see at what densities of SEC it would still be safe to proceed with the cardioversion. Their study involved 1104 persistent atrial fibrillation patients whose current episodes had lasted an average of 87 days. Ten percent of the group had lone AF, 20% had heart disease, and 42% had hypertension. The patients had undergone several different anticoagulation protocols prior to their cardioversion.

- Group 1 – 3 weeks of warfarin with an INR consistently above 2
- Group 2 – short-term (less than 4 days) anticoagulation with low-molecular weight heparin (Enoxaparin)
- Group 3 – 3 weeks of warfarin with at least one INR measurement below 2
- Group 4 – less than 3 weeks of warfarin with an INR consistently above 2

All study participants underwent a TEE within 24 hours of their scheduled cardioversion. Sixty-five patients (5.9%) were found to have thrombi, mostly in the left atrial appendage (LAA), and had their cardioversion cancelled.

The majority of the remaining patients (75.8%) were found to have some SEC with 20% having moderate or severe SEC and 5% having sludge. The severity of SEC was significantly correlated with LAA emptying and filling velocity or, to put it another way, the more sluggish the blood flowed in and out of the LAA the more serious the SEC. Patients with no SEC had an average outflow velocity of 40 cm/s, while those with sludge had an average flow velocity of 17 cm/s. It is well established that LAA in- and out-flow is almost entirely dependent on left ventricular ejection fraction. Those with a normal fraction have good flow in and out of the LAA and thus by inference little or no SEC. Conversely, an impaired left ejection fraction is associated with poor LAA blood exchange and thus a greater incidence of severe SEC, sludge and thrombi.

Surprisingly, there was no evidence that the group with 3 weeks of perfect INR control (on warfarin) had fewer thrombi or less severe SEC than groups 2 and 3. The cardioversion was postponed in 65 patients with thrombi and in 87% patients with severe SEC or sludge. However, the attending physicians decided to proceed in the case of 23 patients with severe SEC and 4 with sludge. Cardioversion was successful in all but one of these patients without thromboembolic events.

Maltagliati, A, et al. Incidence of spontaneous echocontrast, 'sludge' and thrombi before cardioversion in patients with atrial fibrillation: new insights into the role of transesophageal echocardiography. **Journal of Cardiovascular Medicine**, *Vol. 10, No. 7, 2009, pp. 523-28*

Editor's comment: This large study again proves that the risk of clot and sludge formation in patients with normal left ventricular ejection fraction, such as would normally be found in lone afibbers, is indeed extremely low. It, unfortunately, also shows that even perfect anticoagulation for 3 weeks prior to cardioversion is no guarantee that clots will not be present at the time of the procedure.

Tachycardia following AF ablation

BORDEAUX, FRANCE. As more complex forms of atrial fibrillation (AF) are tackled with catheter ablation the incidence of post-procedure atrial tachycardia (AT) is increasing. The incidence of AT following AF ablation is now estimated to be between 5 and 50% depending on the duration of episodes and the type of mapping and lesion sets employed during the initial AF ablation. The AT is often more symptomatic than the afib it replaced, but in 1/3 to 1/2 of cases resolve on their own within a few weeks following the ablation. Unfortunately, AT tends to be resistant to normal antiarrhythmic therapy in which case a follow-up ablation specifically targeting the AT may be required.

Professor Michel Haissaguerre and colleagues at Hopital Cardiologique du Haut-Leveque have just published a two-part report on the mapping and ablation of AT following AF ablations. They now consider this AT a natural progression on the road from afib to normal sinus rhythm and make the following somewhat surprising statement:

> *Conversion of AF to one or more intermediate ATs is an important step in the maintenance of lasting sinus rhythm. Recurrence of AF is rarely seen after this conversion occurs, while it is the most common recurrent atrial arrhythmia when it does not.*

In other words, experiencing atrial tachycardia after an AF ablation is a good rather than a bad sign.

AT can be macroentrant or focal in origin and is often associated with gaps in the lesions made during the AF ablation. The origin of the AT is established by careful electrophysiological mapping.

The first step involves checking that the isolation of the pulmonary veins is complete and, if it is not, filling in the gaps with fresh lesion lines. The second step involves the assessment of cycle length variability to see if the AT is of focal origin, while the third step involves checking for macroentrant circuits, particularly around the mitral valve and in the roof of the left atrium.

A recent study carried out by the Bordeaux group found that 46% of AT was macroentrant, while the remaining 54% was focal in origin (including localized reentry at the pulmonary vein junctions). The average mapping time to determine the origin of the AT was 10 minutes and 97% of all ATs were successfully mapped.

Veenhuyzen, GD, et al. Atrial tachycardias encountered during and after catheter ablation for atrial fibrillation: Part I: Classification, incidence, management. **PACE**, *Vol. 32, March 2009, pp. 393-98*

Knecht, S, et al. Atrial tachycardia encountered in the context of catheter ablation for atrial fibrillation: Part II: Mapping and ablation. **PACE**, *April 2009, pp. 528-38*

Editor's comment: The two articles by the Bordeaux group are most interesting, but highly technical and one has to once again marvel at the knowledge, skill and expertise that goes into bringing an afibber into consistent normal sinus rhythm through catheter ablation. One important take-home message is that "fixing" an atrial tachycardia occurring after a catheter ablation for afib requires careful and highly sophisticated electrophysiological mapping. Thus, selecting an EP using the electrophysiological approach (Haissaguerre and Natale protocols) rather than the electroanatomical approach (Pappone protocol) would probably be preferred.

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