THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation!

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Welcome to this the first issue of a brand new year. I am very pleased to bring you two fascinating articles written by long time subscribers Jackie Burgess, RDH and Patrick Chambers, MD. Jackie attended the Cleveland Clinic Foundation Atrial Fibrillation Summit in October 2005 and has produced a comprehensive report outlining the most important aspects of the presentations made by 20 of the world's most respected electrophysiologists. This month we present the first part. A MUST READ indeed!

As you may recall, Pat conducted LAF Survey 11 last year and has now summarized the results. They provide valuable new insight into the mechanism and possible underlying causes of lone atrial fibrillation. Pat's thorough documentation of a connection between insulin sensitivity and LAF is particularly intriguing. Enjoy!

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Yours in NSR,
Hans

CLEVELAND CLINIC FOUNDATION ATRIAL FIBRILLATION SUMMIT

October 14-15, 2005
Intercontinental Hotel MNBA Conference Center
Cleveland, Ohio

SUMMARY REPORT & OBSERVATIONS – PART I

by Jackie Burgess, RDH

The Conference attracted a capacity audience of 500 Electrophysiologists, Cardiologists, Cardiac Surgeons, Internists and AF Nurses from the US, Canada and several other countries. It was my privilege to attend.

A detailed report from my notes on each presentation can be viewed at http://www.afibbers.com/forum/read.php?f=6&i=17509&t=17509#reply_17509 starting with the very first post and working chronologically forward. I encourage readers to do this since it is impossible to condense all the important comments from my 60 pages of notes. The format allowed 20-30 minutes for each speaker. A minor amount of time followed for Q&A. Some topics were presented in debate form with brief summary rebuttals and questions. Some notes are direct quotes. My personal observations are at the end.

To view the entire agenda and presenters while still available online, go to https://www.clevelandclinicmeded.com/summit/atrial/faculty.htm

OPENING REMARKS
Eric Topol, MD,
Chairman of the Dept. of Cardiovascular Medicine - Cleveland Clinic

"Now that it has become clear that ablating or electrically isolating the pulmonary veins may be curative for some patients with atrial fibrillation, the challenge in going forward is how we can validate and extrapolate this for the future. In order to 'beat' atrial fibrillation, some of the key issues that need to be grappled with include:

- Randomized trials large enough and definitive to prove the efficacy of PVI vs. Medical therapy; there is a desperate need and only one study, currently.
- Determine the appropriate endpoints for 'cure' and what is the long-term efficacy of the available treatments? When can we say it's cured?
- What is the relationship between atrial transport, stroke risk and the need for systemic coagulation?
- Does closure of the Left Atrial Appendage (surgically or percutaneously) really reduce the risk of stroke beyond that achieved by arrhythmia termination alone?
- How long after PVI is anticoagulation required? It's really unknown.
- How can the procedure(s) be refined to be much more practical?
- Is total electrical isolation of the PVs necessary?
- What are the biologic mediators – genes, inflammatory proteins, channelopathies and pathways that predispose to atrial fibrillation (and stroke)?
- Can a better understanding of the biology lead to the identification of new targets and personalized management of AF?

With the continuation of the "Graying of America, "we will continue to see AF increase. We estimate that 25 – 30% of the population will have AF if they live long enough and that the projected number of people with afib will be about double to 5.6 million by the year 2050. Of major concern is the stroke risk that accompanies AF.

What's coming in the future or Beyond Radio Frequency Ablation?

There is a need to find chemical freedom from stroke. There is a heated debate about closure and incomplete closure of the LAA and whether incomplete increases risk of stroke. Do certain types of AF respond better to certain therapies? ie, electrophysiology or surgery? Cryo is definitely being looked at as is a new balloon device. The stent is also a consideration for each pulmonary vein where it provides electrical isolation. Interesting work is being explored with the Vagus Nerve as the new AF target. And, the possibility of potent, anti-inflammatory drugs promises potential.

Conclusion: "Beating Afib is the new frontier of Cardiovascular Medicine."

PULMONARY VEIN ANATOMY – WHAT HAVE WE LEARNED?
Francis E. Marchlinski, MD,
Professor of Medicine and the Director of Electrophysiology
University of Pennsylvania Healthcare System - Philadelphia, PA

Ablations began in the '70's and by the late 90's, EPs came to recognize what cardiac surgeons have always understood – how complex the anatomy is and why it's critical to understand anatomy variations to prevent complications. With the development of appropriate tools, we can prevent complications. Special caution needs to be taken of anatomy either by anatomic mapping (CARTO) or electrical mapping, especially in the relationship of the PVs to the esophagus. It's important to address the risk of collateral damage. We must titrate energy delivery and watch lesion bubble formation to reduce risk of damage to the esophagus.

We know from histology that atrialization occurs in 100% of veins with Afib and 85% without AF; PV atrialization is the rule with or without atrial fibrillation [Atrialization: atrial muscle enters the pulmonary veins (PV) but is not unique to AF]. We know the degree of PV fibrosis affects atrial fibrillation. Is atrialization the result of AF? Anatomy is highly variable and this knowledge is critical.

We know 95% of triggers originate in the pulmonary vein or pulmonary ostium, but as we moved outside the veins and into the antrum and into the adjacent tissue to get away from the stenosis risk, another consideration became important - the collateral damage risk such as to the esophagus. [Antrum: The posterior aspect of the pulmonary veins is thought to blend into the posterior left atrial wall with a funnel shape, referred to as the "antrum" by investigators from the Cleveland Clinic (Ohio).]

Catheter Ablation of Atrial Fibrillation: Pulmonary Veins Antrum Isolation-Demonstration Case
Andrea Natale, MD.
Medical Director Center for Atrial Fibrillation
Co-Section Head – Section of Cardiac Electrophysiology and Pacing Department of Cardiovascular Medicine - Cleveland Clinic, Cleveland, OH

Dr. Natale gave two separate presentations involving his PVAI techniques. Both involved video walk-throughs with his pointing out significant points on techniques, anatomy, and precautions. Questions from the audience were clarified by visual examples and explanations. Following are just a few of the very important points covered. Others can be viewed at the aforementioned site with my complete notes. He stopped during the slides to narrate techniques to avoid collateral damage such as a laryngeal nerve palsy, and how to avoid the phrenic nerve with pace/mapping. He showed an image of phrenic and how, by placing an inflated balloon to push the heart away from the phrenic nerve, damage is avoided. Mentioned using cryo when close to the mitral annulus. Cautioned to be mindful of posterior energy exposure to prevent damage to the esophagus.

Intracardiac Echocardiography Guidance system. (ICE) Value and efficacy demonstrated. Invaluable for accuracy, efficacy and safety of the patient, ICE allows for real-time direct visualization of the pulmonary veins, location of the atrial-venal junction and assurance of the catheter tip location within the pulmonary vein antrum and more. It provides a clear visualization of the transseptal puncture which leads to a critical finding regarding safety.

He identified by ICE image the formation of a clot soon after the transseptal puncture. He said the prevalence of clot formation is so common that they now use a heparin flush before and after the puncture to reduce this occurrence. He showed several examples of the catheter tip with a clot dangling from the end or a clot that had dropped off and was just lying in the atrium. And, he showed a gauze 2x2 on which the catheter tip had been wiped and the many clot fragments that had accumulated. Very graphic.

ESOPHAGEAL FISTULA (EF) is an unintentional burn through the atrium into the esophagus, a serious and critical problem with severe and dire consequences; one that can rarely be corrected by surgical means. Considerable time was devoted to showing the proximity of the back wall of the atrium and the esophagus indicating how easy it is to accidentally cause injury because of the extremely thin heart wall and using too much heat. They have had no EFs at the CCF.

THERMAL MONITORING The importance of adding the thermal monitoring device down the esophagus to a location behind the atria was emphasized. This is now standard in their ablation procedures for tissue temperature control to prevent EFs and provide another view of the area since knowing all the anatomical variances and locations helps prevent mistakes.

Tissue temperature monitoring is critical since even though the energy source is stopped, the tissue continues to heat. The importance of starting with a low energy and ramping up along with the observance of microbubbles to indicate maximum tissue heating was discussed in great detail and pointed out in these video clips with the ICE guidance showing the microbubbles like a little puff of smoke on the screen. Right along with this demonstration was a comparison of what happens with too much heat…formation of holes and craters and irregularly shaped defects in the heart tissue.

A question was asked on how to control microbubbles; the reply was – start low, like 20 – 25 W and titrate slowly. The thought is to minimize excessive use of power to prevent fistula and stroke. He noted that people with lots of scar/fibrosis create more bubbles. On the power issue, he said problems can occur even as low as 10-20 W and added that 50 W is not safe.

PVI vs. PV ANTRUM ISOLATION Antrum is a newer technical term to describe the area of atrium wall farther away from the ostia; he says come out into the antrum and ablates to get away from the stenosis risk. Their ablation procedure ablates the Pulmonary Vein Antrum and the Superior Vena Cava. Between 90 and 95% of all trigger signals or potentials are seen in the area of the PV and the objective of this procedure is "isolation of the antrum."

When flutter occurs after ablation, it was the opinion that ablation scars were either incomplete, not deep enough, or had been so superficial, that nerve conduction recovered.

Regarding paralysis – he commented it was important to pace to be sure the phrenic nerve wasn't captured and paralysis caused. He said they had never seen paralysis, and explained that in some cases (18-20%), they can't completely isolate because of the phrenic nerve location.

The new irrigation catheter is being studied so far with good results. No strokes and it allows increased efficiency (faster).

His final statement included: "We have proven isolation is important."

DEBATE: RATE CONTROL VS. RHYTHM CONTROL: DO WE KNOW THE ANSWER?
Pro:
Alessandro Capucci, MD
Head of Cardiovascular Development - Gugielmo da Saliceto Hospital
Paicenza, Italy

Referencing the AFFIRM study results, his opinion was that a high heart rate is the most important issue. Most patients (77%) are treated for rate. [but he acknowledged that most patients esp. younger, prefer to be treated for rhythm control.] He said it is difficult to treat AF with one strategy because AF is the final result of underlying conditions such as hypertension, hypertrophy, and congestive heart failure. The AFFIRM patients were not very symptomatic and those who could not be cardioverted were also excluded. Pacemaker has poor affect on fibrillation – rate is similar whether rate or rhythm.
Concluding statement: The majority of AF patients come to the MD to ask for a better QoL (Quality of Life). Give them what they do ask by dropping down the ventricular rate. (by rate control.)

Debate: RATE CONTROL VS RHYTHM CONTROL: DO WE KNOW THE ANSWER?
Con:
J. Marcus Wharton, MD,
Professor of Medicine -Director of Clinical Cardiac Electrophysiology
Medical University of South Carolina - Charleston, SC

Early on, rate control was the only method used for AF. We are better now at rate control than years ago but we have even better methods than pharmacology. The AFFIRM study says to treat the symptoms but how easily is this really achieved? The comment was "Relatively" and we must remember that this study population group was either asymptomatic or mildly symptomatic. Control is even harder in the symptomatic. The study says 34% didn't achieve NSR. AFFIRM says 80% of patients are treated by rate control. We are interested in long term NSR. AFFIRM found increased incidence of stroke in rhythm rather than rate, but this was due to the discontinuation of warfarin. We need to stay on warfarin for an indefinite period of time, even if asymptomatic.

We have to consider the costs of rate control. We still have stroke risk (.1%) and intracranial hemorrhage (.3%) along with the high nuisance of side effects (>50%) and decreased quality of life, which is especially true for younger, more active individuals where the significant side effects do affect activity and quality of life since some side effects for some patients are severe; rate control in ventricular problems is limited

Rate control isn't as bad as everyone says; when it works, it's good; often better than anti-arrhythmics but we need to eliminate the negative aspects of pharmacology. Keep patients in NSR and they feel better. If we can get rid of drugs or improve pharmacological results, patients will function better physically and mentally. Rate vs. Rhythm is a Pharmacological treatment. However, Catheter Ablation is clearly superior to pharmacological treatment and allows freedom from drugs and reduces risks and eliminates the negative aspects of pharmacological treatment.

Conclusion: Our goal should be to maintain NSR. It's important to maintain NSR for survival of patients. The risk of asymptomatic afib is relatively high. Our long-term goal 100 years from now should be to get rid of the need for warfarin altogether. Let's get rid of anti-arrhythmics altogether. In a retrospective analysis of the AFFIRM study (Pappone's group), there is indication of direct long-term survival benefits with ablation and getting rid of anti-arrhythmic drugs. Our goals should be rather than using anti-arrhythmics to use more advanced technology to maintain NSR.

COMPLICATIONS OF PULMONARY VEIN ISOLATION –
What is the risk and what can we do about it?

Douglas L. Packer, MD
Co-Director Electrophysiology and Arrhythmia Ablation Laboratory
The Mayo Clinic - Rochester, MN

Damage depends on temperature of the catheter tip and tissue temperature. Tissue temperature becomes much higher than the temperature readings and; once the tissue is heated, it continues on heating. This is of special concern in areas such as PV, esophagus and atrial tissue. Don't turn on to a high degree and expect to control tissue damage.

We control this by using Intracardiac Echocardiography guidance (ICE) and watching microbubbles. When see them, turn down the power. The use of this ultrasound is very important and even then, in some cases, we may not see microbubbles and still have stenosis and the temp can be in the area of 80-100˚ which is much too high.

We have incidence of severe stenosis down around 1% at Mayo which is what Dr. Natale at the CCF also confirms; both use ICE guidance.

Even with stenosis, patients can be asymptomatic or in patients who are initially symptomatic, they tend to be less symptomatic in time. Severe stenosis requires a second procedure of dilation or stenting.

Diaphragm – paralysis: Doesn't happen very often. Mostly avoidable. The phrenic nerve poses a problem and is very easy to damage. It only takes 44˚ to fry the phrenic. Depending on the severity of damage, it can resolve in between 6 and 16 months. The pathway of the phrenic is such that it wraps back behind the RSPV orifice making it very difficult to avoid. Time of application is very sensitive. He maps out the phrenic around 10–20 ma and notes where the whole thing is and paces during the whole time in some cases such as a balloon ablation. Perforation or tamponade – national registry to keep track of (use ICE for surveillance)

Stroke in progress– 0.5 to 2.5%. We should worry when we see sheaths dangling anything (like clots). Like Dr. Natale, we watch with ultrasound and give incremental heparin dosing during the ablation. Is fluoroscopy adequate? Maybe, but it's clear, Mayo's stroke rate is 0.5% using ICE and we think it helps.

Atrial Esophageal Fistula -- unsure how many known occurrences – at least 30; devastating consequences. Esophagus moves substantially during the case so prelim CT scan doesn't mean much. The use of temperature probe provides an additional view and helps define the esophagus (in addition to ICE). Didn't think barium helpful enough to avoid problems. How do you treat esophageal fistula? - - not much experience – very uncertain. Surgical? May be too late even then. Endoscopy could be dangerous.

Conclusion: Be very careful and know where you're heading.

RELATIONSHIP BETWEEN THE LOCATION OF AUTONOMIC GANGLIONATED PLEXUSES AND SITES RECORDING COMPLEX FRACTIONATED ATRIAL ELECTROGRAMS DURING AF

Warren M. Jackman, MD
Professor of Medicine
Univ. of Oklahoma Health Science Center -Cardiac Arrhythmia Research Institute
Oklahoma City, OK

Dr. Packer presented a paper explaining the finding of ablation sites in the right and left atria exhibiting complex fractionated atrial electrograms (CFAE) during AF which suggests there are additional factors important to the success of the ablation procedure besides PV isolation and continuous linear lesions.

One candidate for this factor is the intrinsic cardiac autonomic nervous system. Each of the different ablation procedures apply radio frequency current near the major left atrial clusters of autonomic ganglia or the axons extending between the clusters and the PVs. These clusters are located in the epicardial fat pads and are referred to as ganglionated plexi (GP) by Armour, et al. The possibility that some of the ablation effects may result from destroying GP or their axons is supported by the report by Pappone, et al, identifying a significant increase in short-term ablation success if a vagal response occurred during the RF applications indicating heating of a GP.

Autonomic ganglia are present over much of the epicardial surface of the right and left atria. There may be 7 major clusters of autonomic ganglia (GP) on the atria in humans.

They are testing the ability to localize and ablate GP in patients with AF. This hypothesis is supported by a number of findings.

PULMONARY VEIN ISOLATION IS NOT NECESSARY FOR ABLATION OF ATRIAL FIBRILLATION

Fred Morady, MD
Director, Clinical Electrophysiology Laboratory
University Hospital - University of Michigan - Ann Arbor, MI

The rationale for PV isolation in patients with AF is to eliminate premature depolarizations that trigger AF and to eliminate bursts ('drivers') of tachycardia that contribute to the perpetuation of AF. Circumferential PV isolation was first used by Pappone and although it encircles the pulmonary veins (PV), very often, is not complete isolation and was successful. He showed studies by various EPs with no attempt to isolate PV. Triggers are often still present, so why not AF? They had frequent PACs but no longer had AF. He says not all triggers originate in PV and PVI may not be enough and to check other areas and ablate where necessary. About 28% of triggers occur outside the PV; such as posterior LA wall, Superior Vena Cava, Ligament of Marshall, Coronary Sinus, and acknowledges the success of CCF ablations were because their procedure encompasses many of the extra trigger areas.

His approach is tailored to the patient, not just one particular lesion path but he acknowledges that the PVs play an important role. He said it is important to induce AF or you'll never know where all the drivers are. He said, each case is different and I believe a tailored approach is best.

RADIOFREQUENCY ABLATION OF ATRIAL FIBRILLATION USING STEREOTAXIS TECHNOLOGY
Gabriele Vicedomini, MD
Department of Cardiology Electrophysiology and Cardiac Pacing Unit
Hospital San Raffaele, Milan, Italy

Dr. Vicedomini emphasized the need for what I would term 'user-friendly equipment' reducing greatly the learning curve and also reducing typical procedure time from 480 minutes to 60 minutes. Remote magnetic navigation for AF is safe and feasible with the shortest learning curve suggesting that AF ablation can be

performed even by less experienced operators in low volume centers; ie, Auto Mapping, Auto Navigation to selected points or lines – the computer controls the ablation parameters and end points. Safety benefit: Less pressure on the catheter; “may” have fewer esophageal fistulas, soft contact of catheter tip but very stable, full contact all the time.

Subscribers can access Jackie’s full conference notes at
http://www.afibbers.org/S/jackiesconferencenotes.pdf

RESEARCH REPORT

LAF vs AF: SHAPE MATTERS

by Patrick Chambers, MD

SIZE MATTERS! That has been the banner proclamation for Godzilla and mainstream medicine, when it comes to AF risk. However, the results of LAFS – 11 suggest that shape trumps size and is the primary determinant of LAF risk.

Before proceeding Hans and I would like to thank all of you that took the time out of your busy schedules to complete yet another survey. And I would personally like to thank Hans for allowing me the opportunity to exploit his wonderful resource, all of you. I believe you will find the objective data uncovered by the survey titillating and hope your reaction to the ensuing discussion of that data to be likewise.

What Is Lone Atrial Fibrillation?
Lone atrial fibrillation (LAF) is AF in the absence of structural heart disease (enlarged heart, rheumatic heart disease, coronary artery disease, valvular heart disease, congenital heart disease, etc.). Mitral valve prolapse, frequently encountered in the general population, is not generally considered to represent structural heart disease. Hypertension, which causes the heart to enlarge, is the biggest risk factor for AF in the U.S, according to the American Heart Association (AHA). Some studies on LAF include those with hypertension, while others do not.

Due to the increase in cardiovascular disease with age, once 65 is attained the “lone” is often dropped. Furthermore, aging results in progressive LENGTHENING of the atrial effective refractory period (AERP). NOTE: AERP is the rest period following the contraction of the heart muscle. The cell does not respond to stimulation during this period [1,2,3]. Parasympathetic and sympathetic stimulation can both trigger LAF, because they both cause SHORTENING of the AERP. This is why onset of true LAF after age 65 is most unlikely and why the mechanisms for LAF v. AF may differ [1].

What percent of AF is LAF? The answer to this question depends on what you consider to be organic heart disease and how hard you look for that disease. According to one study, “AF is associated with organic heart disease in 70% to 80% of such patients. AF can occur in the absence of detectable organic heart disease, so-called "lone AF," in about 30% of cases”[4]. “In material based on hospital observations, 35% of all fibrillation was described as being of paroxysmal type”[5]. “About 50% of the patients with paroxysmal AF are lone. This proportion falls to <20% in patients with persistent or permanent forms”[6]. So, these two studies also translate to about 30% of AF being LAF. In other studies a more conservative figure is given. According to the AHA, only 5 to 15 percent of patients with AF have no apparent heart disease or identifiable contributing factor [7].

Because only about 5-30% of AF is lone, most studies on AF make no distinction. Instead AF categorization is limited to paroxysmal (spontaneously terminating and less than 48 hours duration for some v. less than seven days for others), persistent (medically or electrically cardiovertible) or permanent (not cardiovertible).

Could AF and LAF be two different diseases requiring different treatments? Previously differentiation between the two rested on an expensive battery of tests, e.g., EKG, chest radiograph, treadmill test, 24 Holter test, perfusion scan, … Perhaps there is an easier way. Cardiac structural disease may be reflected in body structure, which is much more readily measured. Hence, LAFS – 11 was undertaken in an attempt to explore this possibility and hopefully the results of this survey will underscore the legitimacy and utility of this approach.

Anthropometric Analysis

Anthropometry is the measurement and study of the human body and its parts and capacities. The anthropometric data from LAFS – 11 suggest that LAF and AF are most definitely distinct afflictions and shape not size is the critical parameter. The survey reveals that, whereas pear body shape (gynoid) is good and apple body shape (android) is bad, when it comes to cardiovascular disease risk, the opposite applies for LAF. Furthermore, age at onset/diagnosis, blood pressure and possibly specific lab data may provide further delineation.

RESULTS OF LAFS – 11

	LAFers		Normal Population Means	
	Men	Women	Men	Women
Respondents (77) by gender (%)	79.2	20.8		
Mean present age	58.9	63.6		
Mean age at diagnosis/onset	49.8	53.7		
Mean years of AF	9.1	9.9		
Mean height, inches[8]	71.4	66.6	69.2	63.8
Mean Body Mass Index (BMI)[8]	26.2	24.9	27.8	28.1
Mean waist: hip ratio (WHR)[9,10]	0.91	0.77	0.95	0.88
Mean waist: height ratio (WTR)[12]	0.51	0.47	0.53	0.55
Mean waist circumference (WC)[11]	36.6	31.2	38.8	36.3
Mean blood pressure, mm Hg	121/74			

Statistical analysis of the differences of the means between LAFers and the normal population on all of the above anthropometric measurements range from significant, i.e., p =. 01, (male WTR) to very significant, p < .001, (female BMI and height) to extremely significant, p < .0001, (everything else).

After elimination of several for probable structural heart disease a total of 77 respondents were included in the survey. This included 61 men and 16 women, a 4:1 ratio. Average present age is 59 for males and 64 for females, while the average age at onset/diagnosis is 50 for males and 54 for females (overall mean of 51). Curiously the latter is 50 for all VMAFers. There are many anthropometric measures of cardiovascular disease risk, BMI, WHR, WTR and WC [13]. So, data to calculate them all was requested. LAFers are taller with males and females both being about two to three inches taller than their average counterparts (LAF averages are 71.5" and 66.3" respectively). Regarding BMI, the average male weighed in at 26.2 kg/m2 (includes one BMI over 38), while for the average female BMI is 24.9. The frequency distribution curve for BMI is bell shaped. While BMI is the oft quoted barometer for assessing overweight and obesity, there has been much recently written on waist to hip ratio (WHR) [9,10]. For male LAFers this is .91 and for females it is .77 with an overall average of .88, well under the North American average WHR of .90. However, the latest data indicates that the waist to tallness ratio (WTR) is the most sensitive and specific standard for measuring obesity and related cardiovascular disease risk with limits of .55 for men and .53 for women [12]. WTR for LAFers is .51 for males and .47 for females. LAFers are not hypertensive with an average BP of 121/74. Much of the rest of the data was difficult to assimilate, but there was one other noteworthy result. Only seven LAFers have undergone intracellular mineral analysis, but all seven are either below normal or very near the lower limit of normal for intracellular magnesium. The normal range is 33.9-41.9 mEq/L, and that of LAFers ranged from 30.0-35.0 mEq/L. All of the height, weight, BMI, age, gender and BP results conform to those determined by LAFS – 5 undertaken in 2003.

After analyzing the data from LAFS – 11, a pattern began to emerge and additional data from earlier surveys proved relevant. LAFS – 1 (2001) revealed that 25% of all respondents (50) had hypoglycemia (idiopathic

postprandial syndrome) and another 24% had symptoms of hypoglycemia, yet no one had diabetes. LAFS – 5 (2003) reported the prevalence of diabetes to be 0.6**%** amongst LAFers (v. 6% for the U.S. population). In LAFS –5 the prevalence of hypoglycemia amongst 140 LAFers with vagal or mixed type was reported to be 27% and the prevalence among 24 LAFers with adrenergic type was reported to be 42%.

So, what does this all mean? And what is the link between LAF and hypoglycemia? Hypoglycemia is generally due to either increased insulin sensitivity (decreased blood insulin and glucose levels) or increased insulin. It appears that LAF is highly correlated with **increased insulin sensitivity** and that this may be directly reflected in body shape. The following elaborates on this hypothesis.

Obesity and LAF

The risk of AF increases by 4% for every unit increase in BMI [14]. Since body size is related to heart size and larger atria more easily accommodate AF, the medical literature has linked this increased AF risk directly to increased heart size. This is why AF is often seen in syndrome X (metabolic syndrome) and in the tall, or so it has been reported [15,16]. But this is clearly not the case for LAFers, where increasing BMI over 26 kg/m2 is associated with decreasing LAF risk. Furthermore, the above weight and waist data reflect measurements taken on average eight years after onset/diagnosis. And, of course, these figures tend to go south as we age. In addition progression of episodes over this nine-year period may have restricted any preexisting exercise regimen. This would negatively impact ensuing weight and waist measurements. And finally delineation of LAF from AF can sometimes be quite difficult. Undoubtedly some of the latter may have been inadvertently included in this survey, compromising their anthropometric distinction.

Gender, Age, Blood Pressure and AF/LAF

The 4:1 male to female ratio is difficult to explain. However, LAFS – 11 does contain a clue. The mean age at onset/diagnosis of VMAF in females is a year less than that of male VMAFers. Whatever protective hormone may be at work in females appears to be effective predominantly against the adrenergic component. Age at onset/diagnosis of vagal/mixed/adrenergic types of LAF is 50.3/49.7/49.0 in males and 48.8/58.6/ in females. No female reported pure adrenergic type LAF.

Data from the Framingham Heart Study have established that the prevalence of atrial fibrillation rises with increasing age -- occurring in less than 0.5% of 25- to 35-year-olds, about 1.5% of people up to 60 years of age, and increasing to 9% in people aged over 75 years [17]. This is in contrast to the pattern for LAF where the frequency distribution curve for age at onset/diagnosis is bell shaped with a mean of about 50.6 years.

Hypertension is the biggest risk factor for AF. The relationship between insulin level and systolic/diastolic blood pressure persists after adjustment for body mass index, WHR, norepinephrine, age, smoking, physical activity level, and antihypertensive medication use [18]. Mean blood pressure amongst LAFers is 121/74 mm Hg; ie. well below the range for hypertension.

Hypoglycemia and AF/LAF

In one canine study the AERP was shortest under hypoglycemia in the left atrium and longest under hyperglycemia in the right atrium [19]. Other research indicates that ACTH mediates this through sympathoadrenal stimulation and catecholamine stimulated hypokalemia [20]. Hypoglycemia is a potent stimulant of ACTH secretion [21.22]. Hypokalemia is clearly aggravated by the additional action of increased ACTH driven aldosterone secretion.

According to the Merck Manual on Potassium Metabolism, “Numerous factors affect the movement of potassium between the intracellular and extracellular fluid compartments. Among the most important is circulating insulin level. In the presence of insulin, potassium moves into cells, thus lowering plasma potassium concentration…. Stimulation of the sympathetic nervous system also affects transcellular potassium movement. Beta-agonists, especially selective $beta_2$-agonists, promote cellular uptake of potassium…. High-circulating aldosterone levels lead to increased potassium secretion and kaliuresis” [23]. Insulin, catecholamines (adrenaline) and aldosterone all work to lower blood potassium.

Height and Insulin Sensitivity
Although endurance athletes are typically of average height, tall males also seem to be at increased risk for LAF (Bill Bradley, Akeem Olajuwon and recently 6'4" Mario Lemieux). Since insulin and glucose both inhibit growth hormone (GH) [24], those with increased insulin sensitivity (lower blood insulin and glucose levels) should be taller.

Tallness is a function of growth hormone (GH) secretion during the developmental stage. Growth hormone exerts its effect through insulin like growth factor 1 (IGF-1), produced by the liver. "Tall height and high BMI at 7 yr. were associated with low IGF-1 in adulthood but only in those subjects whose current BMI was below median. On further analysis these interactive effects were particularly strong for height in childhood and adult lean BMI (lean body mass/height^2). Serum IGF-I was positively correlated with fasting glucose, fibrinogen concentrations and blood pressure" [25]. Hence tallness appears to be associated with insulin/IGF-1 sensitivity. As an aside, increased IGF-1 levels have been directly linked with increased cancers of breast, colon, prostate, lung and ovary. Obese men and women demonstrated significantly more deaths due to these cancers, as well as cancers of the esophagus, liver, gallbladder, pancreas, kidney, endometrium, non-Hodgkins lymphoma and multiple myeloma than normal weight controls. The heaviest men were 52% more likely to die of cancer than thin/normal weight men; and the most obese women were 62% more likely to die than thin/normal weight women [26]. LAF seems a small price to pay for extra protection against heart disease AND numerous cancers.

Body Fat Distribution and Insulin Sensitivity
Lower-body obesity in women has been associated with hypoglycemia and a high level of beneficial high-density lipoprotein (HDL). Insulin sensitivity is highest in those with moderate lower-body overweight (11.2), intermediate in controls (6.1) and lowest in those with upper-body obesity (2.6) [27]. Body fat distribution is a more relevant determinant of insulin resistance than obesity. Compared to the normal female, female LAFers appear to carry relatively more of their weight in their hips (WHR = .77). Perhaps female LAFers of normal weight are also relatively insulin sensitive compared to non-LAF females of normal weight.

Thigh fat may contribute to lipoprotein profiles that predict lower risk of cardiovascular disease [28,29]. However, a few LAFers appear to prefer weight lifting to aerobic endeavors. This may not be as beneficial to lipoprotein profile, as demonstrated by one study on HDL levels in professional football players [30]. Weight gain aggravates insulin sensitivity and weight loss improves it [31]. HDL is a surrogate for insulin sensitivity.

Autonomic Tone and Insulin Sensitivity
Our stomachs often remind us when we're hungry. This is because insulin induced hypoglycemia stimulates efferent vagal signals to the stomach. However, a recent study has shown that no simultaneous signals are sent to the heart [32]. Therefore, any role that insulin induced hypoglycemia might play in triggering LAF appears to be more related to subsequent electrolyte imbalance. On the other hand, insulin sensitivity clearly regulates cardiac autonomic tone [33]. These studies suggest that the role of parasympathetic tone in the possible genesis of LAF precedes hypoglycemia [33,34].

There appears to be a substance yet to be isolated, produced in the liver and released by parasympathetic signals, that sensitizes tissue to insulin. It is called hepatic insulin sensitizing substance (HISS)[35]. The HISS hypothesis has been proposed as a new paradigm for diabetes and obesity by Canadian pharmacologist Wayne Lautt [36]. Could this be the missing link connecting parasympathetic tone and insulin sensitivity in LAFers?

Exercise and Insulin Sensitivity/Autonomic Tone
"The proportion of sportsmen among patients with lone atrial fibrillation is much higher than that reported in the general population of Catalonia: 63% vs. 15%" [57]. The prevalence of lone atrial fibrillation in master orienteers was at least six-fold higher than in controls [58].

Physical fitness has also been shown to increase HDL and insulin sensitivity [37,38,39]. In fact HDL (or HDL/TG (triglyceride)) can be taken as a measure of insulin sensitivity [40]. Heart rate recovery after exercise is also related to HDL and can also be taken as a reflection of insulin sensitivity [41], further underscoring the link between cardiac autonomic tone and insulin resistance/sensitivity [42]. On the other hand obese patients have increased sympathetic activity and a withdrawal of vagal activity [43], and these autonomic disturbances improve after weight loss [44,45].

Obesity and Inflammation
Not only is body shape/size intimately tied to hypertension, insulin sensitivity, lipoprotein profile, and autonomic tone but also to inflammation [46]. Commonly used tests for detecting inflammation, e.g., high-sensitivity C-reactive protein (hs-CRP), serum amyloid A (SAA), white blood cell (WBC) count, fibrinogen, are much more frequently elevated in the obese [46,47,48]. These inflammatory markers decrease with weight loss. It has been suggested that a WBC in the upper range of normal is yet another manifestation of the insulin resistance syndrome (syndrome X, metabolic syndrome) along with hypertension, increased cholesterol and increased triglycerides [49]. LAFers may have a white blood cell count at the lower limit of normal.

Inflammation and LAF
Although fibrosis and inflammation have been described in LAF and reactive oxygen species (ROS) generated by endurance sports has been suggested as causative, perhaps LAF precedes the inflammation, unlike in pathologic AF. After all, exercise and HDL are both anti-inflammatory [50] and AF by itself can produce a measurable increase in left atrial ROS [51]. Indirect support for this view may be found in Canadian and Spanish meta-analyses [52,53]. Angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) prevent recurrent and new onset AF in those with structural heart disease, but such findings have not been demonstrated for LAF with or without mild hypertension

Left atrial angiotensin II type 1 receptors (AT1s), but not AT2s are increased in LAFers [54]. On the other hand, pathologic AF is associated with decreased atrial AT1s and increased AT2s [55]. Furthermore, the decrease in AT1s is greater in permanent than paroxysmal atrial fibrillation. Why do the left atrial AT1s differ between LAF and AF? Angiotensin II/aldosterone are prominent players in cardiac remodeling and fibrosis. Therefore, increased left atrial AT1s in LAF should portend greater damage, yet ACEIs and ARBs confer no benefit. Recent research suggests a possible solution to this dilemma. Increased left atrial ATIs in LAF may be no more than a marker for mechanical stress and angiotensin II may not actually be involved [56].

LAF/AF both causes inflammation, whereas perhaps only AF may actually be caused by inflammation. The anthropometric data also support this interpretation.

Alcohol, Glutamate, Coffee and LAF
Alcohol has been well described as a trigger for LAF episodes (holiday heart syndrome). Alcohol-induced hypoglycemia often occurs during the fasting state. Hypoglycemia may result from alcoholic inhibition of gluconeogenesis (creation of glucose by the liver) [59,60] in combination with glycogen (storage form of glucose) depletion. “Light to moderate alcohol intake is associated with enhanced insulin sensitivity and this improvement in sensitivity results in higher HDL cholesterol levels” [61]. Furthermore, the acute effect of a moderate dose of alcohol on the heart is vagotonic [62].

In LAFS – 5 approximately 21% of 166 LAFers associated glutamate intake with initiation of episodes. L-glutamate appears to play a direct role in insulin release, although the precise mechanism remains elusive” [63,64].

Although caffeine has been widely reported to increase insulin resistance (small, short-term studies), long-term coffee consumption decreases insulin resistance. Two recent reports, one epidemiologic study and one meta-analysis, have confirmed this [65], even after adjustment for age, body mass index, and other risk factors [66]. Could coffee aggravate LAF by increasing insulin sensitivity?

Potassium and adrenergic LAF
The risk of AF can be quantified by the equation: wavelength (WL) = AERP x conduction velocity (CV). According to Moe’s wavelet theory, the circumference of each wavelet is > WL and six or more wavelets appear to be required to sustain AF [67,68,69]. Both atrial dilatation and smaller wavelets provide this sustenance. Therefore, since shorter WL => smaller wavelets, shorter WL translates to greater risk of AF. Because adrenergic LAF (ALAF) or stress triggered LAF is associated with sympathetic tone, which causes relatively less AERP shortening (v. vagal tone) and increases CV, then ALAF requires additional arrhythmogenic input. Electrophysiologic studies show that increased dispersion may provide this arrhythmogenic shortfall [70]. Perhaps this is mediated by hypoglycemia. Hypoglycemia not only shortens AERP but also increases dispersion

(heterogeneity) and both are potentiated by hypokalemia. The fact that 42% of ALAFers and only 24% of VMAFers (vagally mediated) are hypoglycemic supports this greater role for hypoglycemia in ALAFers.

The Na-K ATPase pump maintains intracellular potassium in the face of a 30:1 gradient with the extracellular space. The lower the blood potassium levels, the more this pump is challenged and the greater the leakage of potassium from within cells. This "conductance" of potassium forces faster repolarization and hence shortens the refractory period. Therefore, insulin-induced hypoglycemia and its ultimate impact on blood potassium appear to work in tandem with autonomic tone to shorten the AERP. Additional research has shown that low blood glucose increases dispersion of this refractoriness and that this is prevented by the administration of potassium [71]. Blood potassium may be lower in ALAFers (v. VMAFers), because ACTH is not only driven by hypoglycemia but also by stress. This stress mediated ACTH release leads to increased catecholamine and aldosterone secretion. An inability to maintain intracellular potassium in the face of a growing gradient may be at the heart of LAF. In ALAF the gradient may be greater but of shorter duration, whereas in VMAF the opposite may occur (less gradient but longer duration).

Potassium and vagal LAF

In VMAF it may not be the magnitude of the gradient that is critical but its duration, i.e., an extended period of lower range blood potassium. As Hans speculated on p. 63 of *Lone Atrial Fibrillation: Towards A Cure*, the flat or blunted glucose tolerance test curves associated with increased vagal tone may be implicated in LAF. These flat or blunted curves indicate extended periods during which blood glucose is in the lower range of normal. Frank hypokalemia or hypomagnesemia may not even be required for VMAF.

The prominence of nighttime episodes in VMAF may be due not only to increased nighttime vagal tone but also to the midnight diurnal nadir of blood potassium. "Plasma potassium values exhibit a circadian rhythm (average peak-to-trough difference 0.60 mmol/L, with lowest values at night) and also decrease postprandially because of insulin released in response to an ingested carbohydrate load" [72]. Slow leakage of intracellular potassium can also cause muscle cramps and twitching. Twenty one percent of 166 LAFers in LAFS –5 complained of leg cramps, especially at night.

Magnesium and LAF

Intracellular potassium is difficult to maintain in the face of low intracellular magnesium. Magnesium is necessary for proper functioning of the Na-K ATP requiring pump that performs this function. The fact that magnesium was either low or at the very lower limit of normal in seven of seven LAFers undergoing intracellular mineral analysis supports emphasis of its exalted status in preventing LAF episodes. However, the sampling is quite small and no sweeping conclusions can be drawn. Furthermore, this pump is inhibited by digoxin and may explain why digoxin is problematic for LAFers, especially VMAFers [73,74].

According to magnesium expert Mildred Seelig, "Stress causes secretion of epinephrine (adrenaline) and corticosteroids (aldosterone) and results in magnesium loss in animals and in humans. The types of stresses that can increase magnesium needs can be physical (exhausting or competitive exercise, extremes of temperature, and accidental or surgical trauma), or psychological (anger, fear, anxiety, overwork and crowding)" [75,76]. To this list insulin induced hypoglycemia (idiopathic postprandial hypoglycemia) might be specifically added.

Magnesium also impacts cholesterol. According to her book *The Magnesium Factor*, magnesium inhibits HMG-CoA reductase, the rate-limiting step in cholesterol synthesis, thereby working to lower total cholesterol. Furthermore, the insulin to glucagon ratio also influences cholesterol metabolism by either stimulating (high ratio) or inhibiting (low ratio) the activity of this same enzyme [77]. Insulin sensitivity should result in a lower ratio and lower total cholesterol.

SUMMARY

In summary, body fat distribution is inextricably entwined with insulin sensitivity/resistance, lipoprotein profiles, autonomic tone and inflammation. The anthropometric data of LAFS-11 indicate LAFers to be quite distinct in their body shape. LAF (physiologic AF) appears to be the opposite of diabetes, and HDL cholesterol, total cholesterol, triglycerides, BP, WTR, WHR and age at onset/diagnosis may help to differentiate it from pathologic

AF. Elevated total cholesterol in the face of normal BMI and WTR may indicate low intracellular magnesium, especially amongst VMAFers and especially if accompanied by nighttime muscle cramps and/or fasciculations (muscle twitching). Further delineation of the utility of these lab tests in differentiating LAF from AF awaits a future LAF survey (?LAFS – 12). Low blood glucose and potassium appear to conspire in creating an arrhythmogenic substrate. Low blood potassium may represent the final common pathway for both vagally mediated and adrenergic forms of LAF. LAF may represent physiologic AF primarily mediated by low potassium, whereas AF associated with structural heart disease is pathologic AF and predominantly characterized by visceral obesity, cardiac fibrosis and other age related changes.

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