



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			
	<u>LAFers</u>		Normal Population	
	<u>Men</u>	<u>Women</u>	<u>Men</u>	<u>Women</u>
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 beta₂-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/height²). 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 Lutt [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 AT1s 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 (vagal 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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