

THE AFIB REPORT

Your Premier Information Resource for Lone Atrial Fibrillation!

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Welcome to our second issue of 2014, in which we review yet another recent study on the impact of serum magnesium insufficiency. This time, revealing the relationship between low serum magnesium levels 20 years earlier in otherwise healthy individuals from the famous Framingham Heart Study, and their subsequent future development of AFIB.

Next up we review a late breaking study just released from embargo last week from the Missouri Medical Journal with a novel look at the long-term impact of extreme endurance exercise on men who ran at least 1 marathon a year for 25 years while doing 25 to 30 miles of weekly training runs. We have looked before at the downside of too much of a good thing in the form of excess endurance exercise and sports. Yet, this study, and companion review article, wraps the issue up with appropriate balance and evidence that seems relevant for a good number of afibbers who engage in intensive exercise programs.

Our third study review deals with the key issue and debate in AFIB circles on the merits of using Isoproterenol (ISP), an adrenaline-like drug, and/or Adenosine as a drug challenge to confirm that no active triggers are likely to return while one is still on the table during an index or follow up ablation procedure. The majority of US ablation centers now seem to employ ISP challenge while the opposite is true in Europe. It looks like the prevalent EU view may come under pressure here to adapt, as more and more evidence strongly points to the value and potential impact of this protocol in improving long-term ablation outcomes while maintaining a safe procedure.

We also feature a special research report, taking up over half of this issues content, on the important topic of Silent Cerebral Ischemia or Lesions (SCI/SCL) that is a growing focus of research and concern in AFIB circles. These tiny white spots are associated foremost with having active AFIB itself, but can also occur to a lesser degree as an iatrogenic result of catheter ablation, as well as most other invasive cardiovascular procedures. In any event, it's clear the issue warrants an in-depth overview to give our readers the best balance of information we have on how to best minimize the potential impact of SCI.

*This issue wraps up with an overview of two very informative conferences I recently had the pleasure to attend – **EP-Live 2014** in Austin Texas in late February and the **2nd Annual International Symposium on the Left Atrial Appendage** held in mid-March in Orlando Florida. While both were very different in nature, they each covered a broad range of key topics of interest to all of us which we will look at in more detail in future issues. These conferences offered me an invaluable opportunity to hear from, meet and connect with number of top EPs, interventional cardiologists and cardiovascular surgeons from around the world, each sharing their own unique insights and perspectives on this most dynamic and challenging field of medicine.*

I want to remind those subscribers that may rarely visit our website message board of what a rich and dynamic resource it has been for so many over the years, and invite you to drop in more often in-between our bi-monthly reviews here on The AFIB Report. Find us here at: <http://www.afibbers.net>.

Wishing you good health and lots of NSR,

Shannon

Low Serum Magnesium and Development of AFIB in the Community: Framingham Heart Study

BOSTON, MA. We start this issue, once again ... as in our last issue ... with a report on magnesium status and its impact on AFIB. What makes this study particularly interesting is that it examines the broader role of magnesium status in otherwise healthy individuals with no underlying heart disease or history of arrhythmia. This, rather than the association of serum magnesium and AFIB primarily in hospitalized, post surgical patients as in so many previous examinations here. And thus, by design, this recent study focuses on the possible link between low serum levels of this key electrolyte and future development of AFIB over a two decade period, starting with a baseline snapshot of healthy people as part of the famous long-term Framingham Heart Study.

A total of 3,530 participants were selected for analysis after passing the criteria established (listed in the study details) and in addition to a complete medical history, exam and laboratory assessment for cardiovascular disease risk factors at entrance and exit to the study, both fasting serum magnesium and potassium were measured as well as were many other markers at the outset. All participants underwent a 12 lead ECG, and ECG PR interval that were measured manually.

Over the course of the long two-decade study period, all participants were under routine surveillance for the development of AFIB, with all potential cases of AFIB being adjudicated by Framingham Heart Study cardiologists.

Results: The baseline mean age of the cohort was 44 years old made up of 52% women. In men, the mean serum magnesium level at baseline was 1.88mg/dL with a range of 1.44 to 2.40mg/dL. For women, mean magnesium in serum was 1.86mg/dL with a range of 1.15 to 2.46mg/dL.

Over the follow-up period of 18.6 ± 3.7 years, 228 participants, or 5% of the total, developed new-onset AFIB. The age and sex adjusted incidence of AFIB was 9.4 per 1,000 person-years (95% confidence interval [CI], 6.7 – 11.9) in the lowest quartile of serum magnesium, compared with 6.3 per 1,000 person-years in the highest quartile (95% CI, 4.1 – 8.4).

Age and Sex-Adjusted Incidence of AFIB based on Magnesium Quartile

Quartile	Serum Magnesium	Events, n	Person-years	AF Incidence rate 95%CI / 1000 per/yr
Lowest	= 1.77mg/dL	80	17.209	9.4 (6.7-11.9)
Second	1.78 – 1.88	53	16.933	6.9 (4.6-9.0)
Third	1.89 – 1.98	50	15.619	7.1 (4.8-9.3)
Highest	= 1.99mg/dL	45	15.908	6.3 (4.1-8.4)

The study authors note that the association between serum magnesium and AFIB is not a linear one in this cohort of healthy participants at the outset, but follows a threshold with the excess risk of AFIB found primarily in those with the lowest quartile of serum magnesium.

This is not surprising in light of the rather poor correlation between serum magnesium and intracellular (IC) magnesium seen in most studies of the relationship between IC and serum magnesium. The lower the serum magnesium below the reference range limit, the more assured one is of having low IC magnesium stores as well, whereas even within normal range serum magnesium levels, it is not uncommon to find low, to borderline low, IC magnesium driven by the bodies first priority on maintaining a narrow serum range of electrolytes. As such, serum magnesium levels are kept in as tight a range in the blood as possible for as long as possible, by drawing from IC stores in the bones, muscle tissue and organs.

The authors also discovered that with regard to the risk associated with low magnesium status, it appears to be specific for AFIB. Thus, if low serum magnesium was simply serving as a marker for chronic diseases, they would have expected to see an association as well with other illnesses which they did not find in this analysis.

There were several limitations to the study including the obvious issue of a one-time spot magnesium blood test, when magnesium levels fluctuate substantially over time. And yet, a strength of the study is that with such a large cohort followed over such a long time frame, one can conclude that any random misclassification of magnesium status would be expected to bias the results toward the null.

As such, the conclusion is that low serum magnesium is clearly associated with future potential development of AFIB in an otherwise healthy population of mostly European ancestry. If confirmed, this could have major public health implications because of the increasing epidemic of AFIB as well the common and wide spread findings of global magnesium deficiency, which is potentially modifiable by relatively easy repletion via dietary means and supplementation.

Khan, AM, et al. Low Serum Magnesium and the Development of Atrial Fibrillation in the Community: The Framingham Heart Study. Circulation, 2013; 127: 33-38 originally published online Nov 21, 2012.

Editor's Comment: The finding that AFIB predisposition is commonly associated with early signs and signals of metabolic compromise in such a key electrolyte, as indicated by lower magnesium status in otherwise healthy individuals many years before appearance of active AFIB, further underscores the message hammered home here since the beginning of the AFIB Report 14 years ago, recommending restoration of any intracellular (IC) deficiencies in key rhythm stabilizing electrolytes.

Thus, addressing any fundamental metabolic imbalances most plausibly associated with AFIB makes all kinds of sense as a pro-active step we can all adopt early on, and on-going, in our life-long connection with this condition. While we are not suggesting a formal 'cure' here, the evidence now of it being a wise choice to insure healthy levels of the known heart-healthy minerals such as magnesium and potassium is increasingly hard to dismiss.

Increased Coronary Artery Plaque Volume Among Male Marathon Runners - In the long run not so heart-healthy

MINNEAPOLIS, MN. We extend our thanks to the *Missouri Medicine Journal* and Dr. John Hagan MD, past marathon runner and 'afibber', for their timely effort to make us aware of this new research report that was lifted from embargo just in time to make this edition of *The AFIB Report*.

This new study represents one more brick in the wall undermining the long-held sacrosanct idea that long-term marathon running (or other long-term intensive endurance exercise) is unequivocally good for the heart, and offers further confirmation of the association between excessive endurance training and the onset of AFIB, as has been well-noted here in prior issues of *The AFIB Report*.

Male marathon runners (n=50) had completed at least one marathon per year for 25 consecutive years to qualify for the study. All male runners reported no cardiovascular (CV) symptoms and had no CV or coronary history. All subjects underwent coronary computed-tomography angiography (CCTA), 12 lead ECG (electrocardiogram), blood pressure, heart rate and lipid profile readings.

A sedentary matched control group of men (n=23) was derived from a contemporaneous CCTA database of asymptomatic healthy males. The marathoners and controls were all similar in age, resting blood pressure, height, smoking history, serum creatinine, total cholesterol, and low-density lipoprotein (LDL).

Plaque was manually identified and characterized for volume as well as stenosis severity, and CCTA's were analyzed using validated plaque characterization software via a commercial CCTA 3D workstation (Vitre, Vital Images, Minnetonka MN).

The net results of this unique study, being the first to use plaque quantification by CCTA, showed that in spite of a rough equivalence in prevalence of plaque lesions between the marathoners and sedentary control group, the marathoners had, paradoxically, a significantly greater increase in total plaque volume (200mm³ vs. 126mm³ p=0.002), as well greater calcified plaque volume (84mm³ vs. 44mm³ p< 0.0001) and an increase in non-calcified plaque volume (116mm³ vs. 82mm³ p=0.04).

The authors found that long-term marathon running in men over many years paradoxically may undermine the well-proven significant cardiovascular and longevity benefits accrued by more moderate exercise. A 'U' shaped curve is apparent for mortality with respect to the dose of running, wherein the benefits of running were most significant for those jogging, or brisk walking, between 1 and 2.5 hours total a week at a slow to moderate pace over roughly three exercise periods a week. And potentially more detrimental to CV health when running the 25 to 30 miles a week over many years as averaged by the study group of dedicated marathoners showing excessive plaque volume burden as at least one dubious reward for their efforts.

A companion overview article in the same issue of *Missouri Medical Journal* by Peter McCullough, MD and Carl J. Lavie, MD, titled: *Coronary Artery Plaque and Cardiotoxicity as a Result of Extreme Endurance Exercise (EEE)*, does a thorough job of highlighting not only the implications of this latest study on CCTA measured plaque volume in marathoners, but covers a number of recent related findings as well, including adverse effects on cardiac structure and function from EEE, as well as explores the pro-arrhythmic environment of training and competition in which undesirable cardiac remodeling, induced by EEE, can create an arrhythmogenic substrate which can not only increase the risk of atrial fibrillation, but also for dangerous ventricular arrhythmias that can lead to the ultimate adverse event ... sudden cardiac death (SCD).

Missouri Medicine - The Journal of the Missouri State Medical Association, Embargo Date: April 2, 2014

Editors Comments: As with our magnesium study in this issue, this collection of studies on the impact of long time marathon running in males, and participation in extreme endurance exercise over many years, sums up nicely these two areas of practical interest to afibbers that have now both been well-reported on both in past issues of *The AFIB Report*, as well as on our very active message-board.

The bottom-line message here regarding extreme endurance exercise is not that exercise is dangerous for heart health, quite the contrary, but rather that its best to look at it like any otherwise powerful and beneficial drug that has a defined 'U' shaped therapeutic dosing curve. Do too little and you suffer, do too much and you risk undermining all the hard won benefits that should be yours from a more modest and balanced exercise program combining sensible levels of endurance as well as resistance principles. Regular exercise is perhaps the single most powerful health and longevity tool we have. But like most powerful agents for change, too much of a good thing can potentially spoil the party as well.

Administration of Isoproterenol and Adenosine to guide Supplemental Ablation after PVAI

AUSTIN, TX. SAN FRANCISCO, CA. FOGGIA, ITALY. Catheter Ablation, for all its progress over the years, is still associated with significant recurrence of AFIB/Flutter, especially among persistent AFIB patients, and as such, methods to increase success rates are a big focus. This prospective study from one of the leading AFIB ablation/research centers in the world attempts to answer the question: 'Does intra-procedural use of Adenosine and/or Isoproterenol (ISP) to challenge newly formed lesions help uncover non-pulmonary vein (PV) triggers as further ablation targets, and thus improve ablation outcome?'

The study group consisted of 388 participants, divided into 192 consecutive patients with symptomatic AFIB presenting for PVAI (pulmonary vein antrum isolation) ablation in group-1 (n=192), and a separate group-2 (n=196) of matched-control patients also undergoing PVAI, but without drug challenge who were used for comparison. Group-1 patients were administered IV adenosine (18-24mg) and isoproterenol (ISP - 20-30 mcg/min), following PVAI. Additional ablation was performed in those patients in whom adenosine or ISP revealed non-PV triggers that induced AFIB/tachycardia (group-1A n=32-17%). Other subgroups consisted of patients 'with' non-PV triggers that did not induce AFIB/tachycardia (group-1B n=83-44%), and those 'without', that either did not show reproducible foci, or no atrial ectopies, and with no AFIB/tachycardia in response to drug challenge (group-1C n=74-39%).

Follow-up was by standard protocol with success considered to be off all AAR drugs with no evidence of arrhythmia lasting more than 30 seconds at the one full year mark.

A key factor in eliminating non-PV atrial foci is to first be able uncover and locate them, and this can be particularly challenging in both sedated patients or under general anesthesia. After PVAI, drug challenge here revealed a high proportion of non-PV triggers in persistent AFIB cases with 61% of patients showing non-PV triggers out of >80% of the whole group who had persistent AFIB.

Of note, drug challenge had minimal impact in this study group on stimulating 'persistent PV recovery' (less than 5%), after the initial isolation of all PVs. Thus, indicating an impressive reduction in overall intra-procedural PVI reconnections during the index procedure compared to previous reports on that variable. The authors posit that the extent of ablation along the posterior wall in conjunction with the relatively high power used during PV antral isolation in their advanced PVAI protocol may account for the very low rate of PV reconnection observed in spite of ISP challenge.

The net result: targeting non-PV triggers that induce AFIB during ablation results in better outcomes, and that, combined with inability after ablation to induce AFIB with ISP/adenosine challenge is, indeed, associated with improved procedural success at the one year follow-up after an index ablation.

In addition, this study confirmed earlier reports from other top centers that the most common location of non-PV trigger sources were in the LA posterior wall, superior vena cava (SVC), left atrial appendage (LAA), coronary sinus (CS), LA septum and crista terminalis.

Furthermore, and of real interest, the largest subgroup of patients (group-1B) showed consistent non-PV foci that did not induce AFIB during drug challenge while still in the procedure, and who did not receive additional ablation of these non-PV sources as part of this study. Yet, it is telling that this group had an impressively lower success rate of only 34% at one-year follow-up compared to patients in the other two subgroups (group-1A and 1C).

Those in group-1A who got immediate ablation of non-PV triggers that induced AFIB after drug challenge, and group 1C who showed no presence of non-PV triggers under drug challenge, and thus didn't warrant any additional ablation, both had almost identical success rates after one procedure ... 78% in group-1A and 77% in group-1C. This result adds further confidence and credence to the finding that using ISP/adenosine to challenge lesions formed during an ablation leads to better and more consistent outcomes. Keep in mind, that >80% of this total study group were persistent AFIB cases, making the one year single procedure success rates for both groups-1A & 1C impressive indeed.

The clinical significance of these patients producing non-PV foci that did 'not' induce new arrhythmia during drug challenge has been poorly studied and until now remained unclear. Typically, such triggers found previously that did not induce AFIB/tachycardia were not ablated based on a common assumption that they must not be relevant due to lack of triggering AFIB while in the EP Lab. However, these results now reinforce the already growing empirical experience that under ISP challenge, reproducible non-PV sources *not* inducing AFIB in the EP lab will often initiate AFIB under real-world physiologic conditions, and thus require a repeat ablation, if not done so when revealed by ISP during the index procedure.

It is well known by EP's and readers of *The AFIB Report* alike, that AFIB initiation depends on multiple variables including sympathetic/parasympathetic tone, coupling interval of the PAC and/or presence of other co-morbidities like electrolyte imbalances, dehydration and acute infections, as a few examples. And it's been firmly established that while afibbers tend to have many PACs, only a minority of those PACs induce AFIB.

Most studies suggest that treating reentrant arrhythmias, especially around anatomical borders such as perimitral (PMFL) and cavotricuspid isthmus (CTI) flutters, are irrelevant because they are nearly always started by a non-PV source trigger that will start something else, in turn, if left unaddressed. The current study shows that, especially under general anesthesia, targeting only non-PV triggers that induce sustained arrhythmias, while ignoring those that do not induce sustained or repeatable arrhythmia, as has been the rule of thumb norm until recently, no longer appears to be the best approach now that it's clear that even these repeatable foci that are not sustainable in the EP Lab, are often clinically relevant.

Thus, the search for and elimination of non-PV foci, even those that do not induce AFIB during intra-procedure ISP infusion, appears important to achieve better procedural outcomes including long term success rates as an extension of PVAI, particularly for those with persistent AFIB, as noted in this study. *Elayi, Claude S. et al. Administration of Isoproterenol and Adenosine to Guide Supplemental Ablation After Pulmonary Vein Antrum Isolation. Journal of Cardiovascular Electrophysiology, Vol. 24, pp. 1199-1206 November 2013*

Editors Comment: I found this study important as it offers practical criteria for those making a choice for the best ablationist they can find. This report joins several recent studies, including a Chinese work by Zhao, Y. et al, *Catheter ablation of extra-pulmonary vein foci improves the clinical outcome in patients with paroxysmal atrial fibrillation. International Journal of Cardiology, (2014), <http://dx.doi.org/10.1016/j.ijcard.2013.12.292>*, that answer in the affirmative this question: 'should we do drug challenge of new lesions during both paroxysmal as well as persistent AFIB ablations'? More prospective randomized studies are needed to fully confirm these findings, and while it's certainly not the only criteria upon which to make one's choice, at this stage of our knowledge base, it makes good sense to place a strong priority on choosing an EP who employs ISP challenge during their ablations.

Research Report:

Silent Cerebral Lesions: Association with both AFIB and Ablations

In recent years, a growing emphasis and concern in AFIB research has focused on the presence, etiology and ultimate sequelae of Silent Cerebral Events (SCE) or Silent Cerebral Ischemia (SCI). These are tiny white spots, found typically on MRI (magnetic resonance imaging); represent micro-lesions or infarcts deep within the brain that have been thought to be mostly asymptomatic.

In the past, these SCI were presumed to be more or less clinically benign as well, and to-date, no definitive proof of direct cause of clinical cerebral sequelae has been confirmed. Though recent evidence questions just how appropriately the term 'asymptomatic' applies here to SCI lesions, with the increasing 'association' indicated between SCI and cognitive dysfunction and dementia in more recent studies. I emphasize the word 'association' here to highlight from the outset of our discussion, that an association does not inherently imply a direct causal relationship, so please keep that in mind while reading the following.

SCE, by definition, are generally smaller spots =3mm in diameter, which are positively identified via the most sensitive 'diffusion-weighted MRI' (DWI-MRI or dMRI) method, but are negative via 'FLAIR-MRI' processing, which is used to define lesions that result in glial scarring. The somewhat more significant SCI (also called SCL for Silent Cerebral Lesions) tend to be =3mm and are both dMRI and FLAIR-MRI positive indicating permanent glial scar formation and one step closer on the road toward more

symptomatic TIA and stroke manifestation of brain embolism, yet still a good degree shy of either of those more serious diagnosis. [6]

Nevertheless, growing evidence indicates a strong unmistakable association between, not only the presence and number of SCI found in people with active AFIB, but also showing some new additional SCE and/or SCI that has been documented as a direct result of AFIB catheter ablation as well in a number of studies since 2009.

At least one new ablation-related SCI lesion(s) have been reported in a post-ablation range of from 2% to 41% of patients, comparing pre and post ablation dMRI scans in a recent 2014 prospective study. [7] An average occurrence rate of new ablation-related SCI of 14% to 17% was seen in this same report. Indeed, SCIs are often found as a consequence of most invasive cardiovascular procedures including, for example, angiography (15%) and TAVR (trans-catheter aortic valve replacement - up to 68%). [6,]

While these tiny silent white lesions in the brain don't rise even close to the level of clinical or symptomatic concern as do actual strokes and TIAs (transient ischemic attacks), there is growing evidence of an association between the degree of SCI and the presence and severity of cognitive impairment as well as dementia.

Certainly, one can imagine a potential problem from an on-going cumulative burden of even tiny seemingly negligible individual lesions over time. Needless to say, then, this is a topic worthy of real interest and research, and hence, this in-depth overview of the state of our understanding of this issue, circa 2014.

I first reviewed five studies dating from 2009 through 2013 [1,2,3,4,5] looking not only at the presence of SCI and finding a strong independent association with AFIB itself, but also noting its association with cognitive decline and/or dementia in AFIB patients who have not had an ablation, as well as the association of SCI burden with left atrial appendage morphology (LAA) in AFIB patients.

And indeed, all studies so far on this issue have shown a far larger number of people just with AFIB prior to an ablation, having substantial evidence of these asymptomatic cerebral lesions or SCIs, ranging from roughly 60% to around 85%, compared with the much smaller average percentage of 'new' SCIs detected via before and after AFIB ablation MRI scans as noted above (i.e.14% to 17% average range, with 2% to 41% bookends), as documented in the two additional studies (from 2010 to 2014) examining the association between AFIB ablation and creation of new SCEs and SCIs. [6,7]

The key point emphasized throughout this report to keep in mind, is that the risks of increasing SCI burden are far and away greatest while living with active AFIB, be it paroxysmal or persistent, though not surprisingly with an added burden seen in persistent cases. And, importantly, any added SCI burden one might accrue from an AFIB ablation seems to be significantly lower than the on-going cumulative SCI burden from living with uncontrolled AFIB [2,3,4,5].

As outlined below, the bottom-line of this scenario seems like a good fit for the wise old analogy: 'It often takes a smaller thorn to remove a larger thorn'. So let's now look at this issue in more detail.

The Case for SCI and AFIB

The debate seems settled for the clear association between not only on-going paroxysmal and persistent AFIB with an increased risk for a cumulative burden of SCI's associated with an increase in AFIB burden, but also for an added risk of developing and worsening cognitive decline which also increases in association with duration of active AFIB.

This observation isn't surprising because both disease states of dementia and AFIB share similar background risk factors, and furthermore, AFIB has been independently linked to memory impairment, cognitive decline and general dementia in patients without pre-existing disease. [2]. As such, it is

possible the two conditions coexist due, perhaps, to a common shared underlying etiology such as an, as yet, unidentified inflammatory vascular dysfunction, for example.

The experienced Intermountain Heart Rhythm Group out of Salt Lake City Utah, concluded in late 2009 that AFIB was clearly associated with all forms and subtypes of dementia from a large database of 37,025 patients over a 5 year follow-up period, with 10,161 (27%) of the total study group developing AFIB and 1,535 (4.1%) developing dementia over this period.

Of particular interest, was the finding that although dementia is strongly associated with aging, the highest risk of AD (Alzheimer's disease) was in the younger group of AFIB patients, in support of the observed association. The presence of cognitive decline and dementia occurred earlier in those with AFIB versus no-AFIB, and the association with AFIB also identified dementia patients at high risk of death.

In a more recent 2013 meta-analysis out of St David's Medical Center in Austin, that included the same large prospective observational study from Utah as one of 8 other similar comparative prospective observational studies, gave greater weight to the overall association between AFIB and dementia and better facilitates extrapolation of these findings to the general population.

Out of a total of 77,000 patients enrolled in the 9 total studies in this meta-analysis, 11,700 (15%) had AFIB, but with normal cognitive function, and with none having suffered an acute stroke at baseline. A key aim of this study was to confirm the previous association between AFIB and risk of developing or worsening dementia not only in patients after an acute stroke, or in those who already had some degree of cognitive impairment, but in particular to see whether AFIB also increases risk of dementia in patients with normal cognitive function and without a stroke history which had previously been unclear.

The sum total of this meta-analysis confirmed that AFIB significantly increases risk of developing dementia over the respective follow-up periods, independently from other baseline confounders. Thus, these results underscore and add important information to the association between AFIB and dementia, strongly supporting an independent longitudinal relationship between the two conditions. [4]

The authors of this meta-analysis also noted that, "from a pathophysiologic viewpoint, the inherent risk of cerebrovascular thromboembolism, including silent embolic events, together with global brain hypoperfusion resulting from impaired cardiac hemodynamics, may account (at least in part) for the increased risk of developing dementia in AFIB patients.

In other words, its likely micro-embolic or micro-ischemic events too small to detect with a TEE (trans-esophageal echocardiograph), perhaps in combination with possible subtle blood flow restrictions to the brain over time resulting from impaired cardiac function and pumping action during AFIB, could be at least two drivers for developing or worsening dementia in those with AFIB.

And yet, it also is possible that both conditions primarily result from an, as yet, undiscovered underlying vascular dysfunction, likely inflammatory in nature, that drives both AFIB and dementia as speculated earlier. And we can't rule out all of the above possibilities as potentially contributing together, or separately, toward this close association we see between AFIB, cognitive decline and dementia.

Whatever the relationships turn out to be, with the huge financial, physical and emotional burdens both conditions impose on individuals, their families and society as a whole, its little wonder why this connection has moved recently to front and center in AFIB research centers around the world. Future studies are warranted to establish if there really is a direct causal relationship between AFIB and dementia, as well as better define to what degree SCI burden might factor into the equation. And to establish whether effective treatment of AFIB might reduce the risk of developing dementia as well.

A January 2014 study from the same group above in Austin looked deeper into this connection between patients with AFIB while investigating whether there was any connection between left atrial appendage (LAA) morphology and SCI burden. This investigation found such an affirmative association, not

surprisingly, just as they had found a correlation between actual stroke and TIA risk and LAA shape in an earlier 2013 landmark study. [5].

When looking at SCI burden in correlation with LAA morphology, out of 348 patients comprising the study and presenting for MRI prior to an AFIB ablation, 295 (84.8%) showed a median number of 23 SCI lesions in their brains. And indeed, SCI burden was related to LAA complexity; with the simpler less complex 'cactus' and 'chicken wing' shape having a somewhat lower overall SCI burden, while the more complex shapes 'windsock' and 'cauliflower' had the greatest correlation with increased SCI burden. Only age and LAA morphology related to SCI burden in AFIB patients. This, too, more or less mirrored the correlations found between stroke and TIA with the various LAA shapes as well in that earlier study.

Silent Cerebral Events and AFIB Ablation

Having already established a solid association between on-going paroxysmal and persistent AFIB and the future development of cognitive decline and dementia, as well as between AFIB and an increasing SCI burden, the issue of additional SCE and SCI burden having also a direct iatrogenic cause, via the AFIB ablation procedure itself, adds another important wrinkle to the equation.

And although there are, as yet, no proven sequelae related to the presence of these SCI spots, we can't rule out the possibility, or even likelihood, of a cumulative subtle neuropsychological impact. Reinforcing that possibility, a recent in-depth study by Gaita, et al, at his Italian center showed that patients with AFIB and a positive finding of asymptomatic SCI on MRI have worse cognitive performance compared to matched patients in sinus rhythm without AFIB. Hence, until we garner more definitive insight into the exact mechanisms and long range impact from SCI, its clear we should aim as much as possible toward a goal of 'zero SCI burden'.

Fortunately, much work is already underway in that regard with respect to lowering SCE and SCI burden during an ablation procedure, and with some impressive success so far, particularly from the renowned Austin, San Fran, Italian group as demonstrated in their most recent study from March 2014 ... the first large prospective study seeking to detect SCI via 'diffusion-weighted MRI' after RFCA (radio frequency catheter ablation) employing an open-irrigated catheter while on uninterrupted anticoagulation. [7]

While we aren't entirely sure of the direct cause of these tiny cerebral lesions during an ablation itself, it stands to reason they arise from multifactorial issues such as either tiny gaseous or particulate embolic events during the procedure, even with some indication of possibly being more likely to happen in those with more extensive fibrosis and structural remodeling. [6]

So far, different factors associated with higher rates of SCI that have been identified in three categories, including 'patient-specific issues' such as LA dilation and fibrosis, 'ablations technology related factors' like using older non-irrigated versions of both single electrode catheters, or non-irrigated multi-pole phased RF catheter systems, the later two adding greater risk for SCI compared to safer open-irrigated catheters.

The final category that may impact SCI generation are 'procedural/technique related considerations' including use of double vs. single LA trans-septal puncture and choice of intra-procedural anticoagulation regimen, as well as either settling for the riskier 250sec or below ACT (activated clotting time) or insuring strict control of ACT above 300 to 350sec from just prior to trans-septal puncture and throughout the remaining time catheters and sheaths remain in the left atrium (LA), all seem to have a real impact on amount of SCI created during an ablation.

The good news is that this brings with it real opportunity for lessening the addition of peri-procedural SCI lesions during ablation, and warrants looking at a bit further.

Those ablation groups and EPs who use a double trans-septal puncture with a separate sheath for both the lasso mapping and ablation catheters, avoid having to switch those two catheters in and out of one sheath repeatedly during the procedure, as happens when only a single trans-septal puncture is used.

What might happen, is that when several or more catheter transfers take place via a single sheath, it's possible the tiny one-way valve within a sheath might wear out, leading to micro-gaseous bubbles or emboli entering the LA unexpectedly, or possibly micro-sized thrombotic emboli too small to detect with intra-procedural imaging and might get knocked off the end of a catheter during repeat transfers in and out of a sheath, and might then travel from the heart and to the brain causing a tiny SCI lesion.

In any event, such a scenario is less likely to occur with a dual trans-septal puncture using a dual sheath protocol, thus minimizing catheter transfers in and out of the LA. [6]

Unbroken Peri-procedural Anticoagulation Appears Key

However, what appears to be the single biggest contributor toward minimizing SCI creation during an ablation in addition to open-irrigated catheters, is maintaining a continuous unbroken anticoagulation protocol beginning approximately 4 to 6 weeks prior to ablation extending through the full ablation itself. And which is then continued after the ablation upwards of two months or more, as needed.

This protocol, has been championed and developed by the same St David's Medical Center/CPMC/Cleveland Clinic group, among others, and typically employs continuous therapeutic levels of warfarin, including throughout the actual peri-procedural period and afterward. Warfarin, which more recently has increasingly been replaced by Xarelto as an alternative, is augmented during the ablation with a large 8,000IU to 10,000IU heparin bolus infusion started just prior to trans-septal puncture to insure maintenance of an ACT of at least 300sec or a bit higher.

Some debate continues over just how high the ACT needs to be maintained while catheters are within the LA, but it is typically much easier to achieve a somewhat higher ACT level when employing an unbroken continuous anti-coagulation scheme in any event, and the results here from the latest study to directly compare continuous unbroken anti-coagulation using IV heparin and maintaining an ACT = 300sec, versus both a compromised continuous protocol and with interrupted warfarin bridged with enoxaparin plus IV heparin at trans-septal puncture, speaks for itself.

New SCI seen on dMRI resulting from the ablation itself in this study dropped to a very low 2% (3 of 146 patients) for group-1 using continuous anti-coagulation with warfarin plus the large IV-heparin bolus before trans-septal puncture and holding ACT = 300sec, compared to new SCI found in 7.4% (10/134 patients) in group-2 that attempted a full continuous anti-coagulation protocol, but either failed to maintain a therapeutic INR the entire time prior to the ablation, failed to receive an adequate pre-transseptal bolus of heparin, and/or failed to maintain an ACT reading = 300sec for two consecutive readings after trans-septal puncture.

However, for group-3 (21/148 patients) which stopped at least one month of therapeutic levels of warfarin 3 days prior to ablation, and then bridged with bw-molecular weight heparin (enoxaparin), during the ablation itself, augmented with a 15,000IU IV-bolus of heparin prior to trans-septal puncture, followed with 1,000units/hr heparin adjusted to maintain an ACT= 300sec for the rest of LA access, the presence of new iatrogenic SCI lesions was 14% versus only 2% for group-1 with the unbroken warfarin plus heparin protocol!

Therefore, it's not so surprising that this tried and true protocol of continuous anti-coagulation which has been a cornerstone leading to significant reductions in stroke and TIA risks from ablations at a number of top ablation centers, would have such a significant impact on lessening SCI generation as well.

Consider that with persistent AFIB ablation, which brings with it a somewhat greater risk for SCI generation, and the greater likelihood of needing two procedures in total (or occasionally three) to get the job fully done even with an expert ablationist, it's all the more important to keep SCI burden in each procedure to a minimum.

And thus, a real priority should be placed on choosing those centers and EPs that first and foremost, not only, have superior experience and track record with your kind of AFIB, be it paroxysmal, persistent or long standing persistent ablation, but also who employ open-irrigated catheters, and maintain an unbroken anti-coagulation protocol as top priorities. At this point in our evolving understanding, it appears too that maintenance of an ACT = 300sec while inside the LA, as well as preferably using dual trans-septal punctures and sheaths to minimize catheter transfers, may also pay added dividends in terms of lessening iatrogenic SCI risks. Thus, consider including these criteria as part of your litmus test, and it should help stack the odds in your favor for an excellent choice of ablationist for your procedure.

Consider as well including in your decision tree as a key priority, those EP's that also employ isoproterenol/adenosine drug challenge during their procedures, as noted previously in this issue of our newsletter. A step that is proving to be an invaluable tool in promoting higher long-term success rates and, as such, could well result in a reduction in total number of procedures required and more time spent in NSR. And, in turn, should help reduce the risk of additional SCI burden long term.

Take Home Message

Taken all together, we've discussed some solid additions to one's overall criteria to use when narrowing down your search list of highly-skilled ablationists who, in addition to focusing on top quality near term ablation results, also pay close attention toward reducing potential long term risks for the patient.

Keep in perspective that we don't yet know for sure what, if any, true long-term consequences these tiny SCIs may have on AFIB patients. However, it does stand to reason via all that we do now know from the strong associations discovered in recent years, that aiming toward minimizing both SCI burden, as well as frank stroke and TIA risks, while moving toward a 'zero-risk' ideal for all three should be our collective goal.

Real progress has been made by EPs and centers that already employ all of the best prophylaxis we know of, not only for greatly reducing stroke and TIA risk, but also significantly curbing ablation-related silent cerebral events or lesions, as indicated in the meta-analysis study above.

However, should you need an AFIB ablation, don't let the possibility of some degree of iatrogenic-related SCIs from the procedure deter you from seeking out the best expert EP and center you can find, and instead choose to remain in either paroxysmal or persistent AFIB on that account. AFIB itself remains your greatest obstacle for minimizing the potential accumulation and impact of SCI and frank stroke or TIA risk long term, and along with it the potential for greater risk of cognitive decline and dementia. As noted EP and ablationist Dr. Peter Weiss of Utah's Intermountain Heart Rhythm Center shared with me in a conversation recently regarding this issue:

"Just as an increase in 'AFIB burden' is associated with increased stroke, TIA and SCI risk, so too, an increase in 'NSR burden' appears associated with a decreased risk of those same issues. So the best methods of achieving the greatest duration and durability of time in NSR should be our focus, even with some acceptably low risks from a procedure like an skillfully-performed ablation, which can be so effective at dramatically increasing as much NSR time in one's life as possible".

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EP-LIVE 2014 & 2nd Annual International Symposium on the Left Atrial Appendage (ISLAA) - Overview

It's been a whirlwind first three months for me since taking over the reins at *The AFIB Report* and <http://www.afibbers.org> website. I've been fortunate enough to attend three very interesting AFIB related conferences during this time, including *Boston AFIB in Orlando* last January, *EP-Live 2014*, a two day live intensive real-time education and training seminar for EPs and Fellows held at the prestigious world class ablation and research center at St. David's Medical Center in Austin Texas. And most recently in mid-March, The 2nd Annual ISLAA also in Orlando, that was very interesting and informative, even exceeding the high expectations I had for the event before arriving.

With a rather full issue at this point, rather than highlight the main issues discussed at these two conferences, we will save those for a future issue and end this edition with an overview of the real-time ablations event in Austin and the 2nd Annual ISLAA conference in Florida.

EP-LIVE 2014

Was graciously hosted by Dr Andrea Natale and ten expert EP colleagues as well as their large and very capable staff at Texas Cardiac Arrhythmia Institute and St David's Medical Center. The format was two intensive days of live EP procedures being broadcast either from their four state-of-the-art EP labs to a large amphitheater conference and education facility, or via pre-recorded session from those EPs not physically present. These folks really know how to put on a conference!

The videos were screened via a compilation of multiple large LED panels combined as one and stretching across the entire front wall of the amphitheater, hosting multiple video feeds at once from every mapping and imaging system being used in a given procedure. Also, live video of a given procedure was shown while the operating EP described in detail just what they were doing at each step of the way.

The dialogue between some of the top ablationist from all over the US, and a few leading European and South American EPs as well, back and forth in real-time, with the operating ablationist was lively and a great learning experience even for a former patient such as myself. For the experts and fellows alike, it was a fabulous opportunity to learn by exchanging ideas and experiences on the very cutting-edge of this most vibrant and exciting field of medicine that I know of.

2nd Annual International Symposium on the Left Atrial Appendage

Having experienced my own LAA ligation with a Lariat procedure last August, I was especially interested in what might be shared during a three day conference dedicated to all things regarding this often overlooked appendage, described as 'the most lethal appendage in the human anatomy'.

One might think they would run out of things to say about this small dead-end side chamber opening into and hanging off the upper left front side of the left atrium, but one couldn't be more mistaken!

Dr Dhanunjaya Lakkireddy, former Natale protégé, and for the past 8 years head of his own very active group of smart EPs and AFIB researchers, including a dedicated Interventional cardiologist in Dr.

Matthew Earnest as part of their team, comprise a formidable ablation and research center at University of Kansas Medical Center in Kansas City. Somehow, they also find the time to organize and play key host, along with Drs. Natale, David Holmes, Vivek Reddy and Saibal Kar as co-directors of these now annual symposiums dedicated to enlightening the cardiology world about the underappreciated importance of the LAA in not only stroke risk management, but in understanding and addressing arrhythmogenesis and improving overall heart health.

However, it's really Dr Lakkireddy and his team that is most responsible for the ISLAA, and playing such expert hosts to speakers and participants alike. I was mightily impressed by Dr Lakkireddy, not only for his breadth of knowledge, but for his obvious enthusiasm and energy for cutting-edge AFIB and ablation research and fostering physician education. His whole crew including Drs. Ryan Ferrell, Loren Berenbom, and Madhu Reddy, all deserve special mention for helping to pull off a highly professional and rewarding symposium. And last, but far from least, there is event manager Donita, without whom the conference would never have been so smooth and successful.

In any event, I now understand how they run a first class ablation program at KU Medical Center. Good news for any who are looking for AFIB expertise in that part of the country.

One talk in particular that struck me at the ISLAA was by world-renowned icon of interventional cardiology Dr David Holmes of Mayo Clinic. He addressed us all saying that we would not, in the present, be able to fully appreciate the seminal significance of what was happening in this conference, and within this new movement toward deeper appreciation of the LAA with its multi-level influence on cardiovascular and overall health.

Not until many years hence, said Dr Holmes, when we all look back and remember that we were there when this dynamic seed of cooperation was first planted between EPs, interventional cardiologist and cardiovascular surgeons, with all three sub-specialties represented by some of their leading practitioners, in all coming together to encourage a team approach to best improve outcomes for patients.

You really could feel the sense of excitement and energy there with so many different ideas and approaches to a similar problem being discussed and debated among all three major branches of cardiology that typically would be hosting their own separate and isolated conferences to discuss the same issue. In any event, patients will be the ultimate winners from this on-going collaboration. And thus, kudos to Drs. Lakkireddy, Natale, Holmes, Kar and Reddy for insuring this focus will continue to blossom with a 3rd Annual ISLAA already schedule for February 2015 in Los Angeles.

Two major topics at ISLAA focused on the growing field of LAA occlusion/ligation/excision, as well as in-depth examination of stroke prophylaxis with the new novel oral anti-coagulants (NOAC) compared to warfarin, and every issue you can imagine relating to their use. Fortunately, and with a little luck, in two years we should have what appears to be a relatively safe and effective reversal agent, at least for the Factor-Xa drugs like *Xarelto* and *Eliquis* as well as the newest NOAC poised for approval before long, *Endoxaban*.

One thing that was obvious, is that the LAA ligation and exclusion scene is on the verge of exploding with greater experience now on the books for both the *Lariat* (with over 2,000 procedures now done) and the *Atriclip* with a minimally-invasive EP-accessible approach promised soon. Also, with the Watchman moving toward hopeful FDA approval soon and others like the Wavecrest LAA occluder that is similar to the Watchman in concept, but with some nice design wrinkles and likely to be close on the heels of Watchman approval.

Nevertheless, we'll have to wait to explore more on these and other issues in a future issue of *The AFIB Report*. In the meantime, be well and a quiet heart for you all!

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