

VIRTUAL LAF CONFERENCE

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SUBJECT: LAF and the Hormone Connection II

We have danced around aldosterone, angiotensin, atrial natriuretic peptide (ANP) and inflammation in the pathogenesis of AF for several years now. In view of recent data it may now be possible to "connect the dots". One mea culpa for its length and another to those that find it too complex.

This post is not an attempt to tackle the complex autonomic determinants of episode onset, which is probably due to "accentuated antagonism" (see Sessions 35 and 37 in the CR Proceedings). It only outlines a plausible predominantly hormonal mechanism via which LAF/AF episodes may be triggered and deteriorate over time.

In mid December 2002 in the BB we started a thread on ANP. At that time (12/10/02) Hans contributed much of the below to the discussion. Indeed that BB topic in part led to "The Play" by Hans Larsen (see CR Session #2, LAF and the Hormone Connection, 1/15-1/31/03). I've included additional more recent research findings and balanced the discussion to include information on ANP's antagonist angiotensin/aldosterone.

ANP

- Atrial cells secrete ANP during tachyarrhythmia (AF or tachycardia)
- ANP inhibits aldosterone secretion due to the renin angiotensin system (RAS), ACTH or K⁺ in a dose dependent manner. <http://ajprenal.physiology.org/cgi/content/abstract/258/3/F473>
The renin angiotensin system (RAS) provides the lion's share of aldosterone.
- Another group of Japanese researchers found that ANP and BNP not only increase sodium and water excretion, but also inhibit cortisol production in a dose dependent manner.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1659877&dopt=Abstract
- ANP/RAS activity are stimulated during exercise.
<http://jap.physiology.org/cgi/content/abstract/76/5/1882>
<http://physiology.umc.edu/themodelingworkshop/Integrative%20Model/Foundation%20Data/Physical%20Exercise/Renin-Angiotensin/Renin-Angiotensin.HTML>
Perhaps frequent prolonged aerobic training sessions (physiologic tachycardia) serve the same function as multiple episodes of AF, at least wrt ANP/RAS stimulation.
- ANP is a marker for salt sensitivity.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12019282&dopt=Abstract
- ANP released during submaximal exercise in chronic AFers predicts a better chance of staying in NSR after cardioversion.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11139947&dopt=Abstract

- Japanese researchers found that ANP levels decline with increased duration (years) of AF. They ascribe this to a failure of the atria to produce ANP because of degenerative changes (fibrosis).
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11788221&query_hl=10
- Left atrial fibrosis is increased in LAF (v. controls).
<http://heart.bmjournals.com/cgi/content/full/90/4/400>
- Italian researchers found that one of the most important predictors of spontaneous conversion to NSR was a high level of ANP.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10922452&dopt=Abstract
- They also found that people whose LAF attack occurred during sleep had a seven-fold higher probability of spontaneous conversion during the first 24 hours than did those whose attacks occurred during the day.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10922452&dopt=Abstract
Is ANP higher in VMAFers than in ALAFers?
- This same Italian research group showed that patients with a high blood level of ANP were 3.2 times more likely to experience a spontaneous conversion than were patients with lower levels.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10922452&dopt=Abstract
- ANP levels in young women average approximately twice those in young men, but in postmenopausal women ANP levels are not greater than those in age-matched elderly men.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2137132&dopt=Abstract
Could this, at least partly, be responsible for the lower incidence of AF among premenopausal women? Estrogen also possesses calcium channel blocking properties independent of ANP.
- BNP levels are also higher in females, and females (and males) with LAF have higher BNP levels during NSR than controls.
http://www.diavant.com/diavant/CMSFront.html?pgid=1_10006_10006_1
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=15629379&dopt=Abstract
Increased BNP would also drive elevated opposing RAS activity, i.e., increased AT1s (see bullet #1 under angiotensin).
- German researchers have reported that ANP has anti-inflammatory properties and inhibits the release of inflammatory tumour necrosis factor alpha and interleukin 1 beta.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11890659&dopt=Abstract
Could the gradual decline in ANP as AF deteriorates partially explain the AF inflammation connection?
- ANP inhibits L-type calcium channels in the rabbit heart, thereby limiting intracellular calcium.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7540093&dopt=Abstract
Increased intracellular calcium activates several potassium channels that lead to shortening of the AERP. Furthermore, the adaptive mechanisms addressing this intracellular calcium overload come at the cost of additional AERP shortening with “loss of physiologic rate adaptation”.
<http://dissertations.ub.rug.nl/FILES/faculties/medicine/1999/r.g.tieleman/c10.pdf> p. 172
Could the gradual decline in ANP as AF episodes increase in frequency and duration be the mechanism whereby “AF begets AF”?

Angiotensin

- In LAF (v. normals) left atrial angiotensin II type 1 receptors (AT1s) are increased.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14642689&dopt=Abstract
Could these AT1s be increased in LAF because increased RAS activity is necessary to oppose the action of increased AF induced ANP? Could VMAFers have increased left atrial AT1s to accommodate RAS activity necessary to oppose

increased exercise induced ANP? What about RAS and dehydration during prolonged exercise?

- Participation in endurance sports markedly increases the risk of AF.

<http://eurheartj.oxfordjournals.org/cgi/content/abstract/23/6/477>

<http://bmj.bmjournals.com/cgi/content/short/316/7147/1784>

Over time one can only imagine how much greater is this chronic exposure to renin (and angiotensin II) in those that participate in endurance sports (v. controls) with or without associated dehydration. Prolonged exercise induced inflammation (and fibrosis) would be another consideration.

- Angiotensin II type 1 receptors mediate shortening of the AERP (as does increased autonomic tone), predisposing to AF. Angiotensin II type 1 receptors also mediate fibrosis.

<http://dissertations.ub.rug.nl/FILES/faculties/medicine/2003/l.j.wagenaar/c1.pdf>

- Angiotensin II is vagolytic.

<http://heart.bmjournals.com/cgi/content/full/80/2/127>

If both AT1s and increased vagal tone cause shortening of the AERP, this leads to the obvious question "What is the net effect of angiotensin II on AERP".

- ARBs, unlike ACEIs, do not appear to be vagotonic.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=11724639

This suggests that the predominant effect of angiotensin II is vagolytic. Nonetheless angiotensin II causes AERP shortening via AT1 receptors. With ACEIs (e.g., lisinopril) there is theoretically no production of angiotensin II. With ARBs (e.g., candesartan) angiotensin II should be increased but it cannot attach to its AT1 receptor. My own brief experiment with lisinopril (ACEI) resulted in exacerbation of my VMAF episodes. Given the above, perhaps candesartan (ARB) rather than lisinopril (ACEI) would have been a better choice for VMAF.

- During transition from paroxysmal to permanent AF in those with structural heart disease (i.e., not LAF) atrial angiotensin II type 1 receptors are progressively downregulated and atrial angiotensin II type 2 receptors are progressively upregulated. <http://circ.ahajournals.org/cgi/content/abstract/101/23/2678>

Cardiac ANP production is probably slowly compromised due to increasing fibrosis (see bullet #7 under ANP). In this manner could the RAS gradually gain the upper hand in its tug of war with ANP? Fewer AT1s would be needed to counter the effects of declining ANP.

- Angiotensin II type 2 receptors (AT2s) are cardioprotective and are histologically clustered around fibrous tissue.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8877788&dopt=Abstract

<http://hum-molgen.org/NewsGen/12-2004/msg19.html>

Perhaps sufficient fibrous tissue stimulates the proliferation of AT2s, explaining the discrepancy between their presence in AF but not LAF.

- Due to decreased cardiac output in those with structural heart disease RAS activity (and cardiac fibrosis) is increased. Perhaps the gradual escalation in fibrosis induced dispersion of refractoriness, conduction velocity, etc., explains the age related increase in AF.

- ACEIs and ARBs prevent recurrent and new onset AF in those with structural heart disease but not in LAF with or without mild hypertension.

<http://www.medscape.com/viewarticle/493281> (11/04)

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=15936615&dopt=Abstract
(6/2005)

Discussion

The above research findings provide a plausible argument for a central role of ANP/RAS in the maintenance and progression of LAF/AF from paroxysmal to permanent.

Do the increased left atrial AT1 receptors in LAF represent cause or effect?

Perhaps frequent prolonged exercise (or any tachycardia) and concomitant release of ANP (and RAS activity) drive this increase in opposing AT1s. If this were true, then one would expect decreased RAS activity in the physically fit (v. controls) during NSR. Such is the case.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3280723&dopt=Abstract

One would also expect increased RAS activity during exercise in the physically fit (v. controls). Such is also the case.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9263619&dopt=Abstract

But what about adrenergic LAF. Perhaps their baseline ANP/RAS activity (v. normals) is somehow accentuated (?stress related), thereby driving production of increased atrial AT1 receptors. Stress is the trigger for most ALAF episodes and this is accompanied by an increase in aldosterone, cortisol and catecholamines. ANP inhibits cortisol production (see bullet #3 under ANP). Perhaps cortisol also plays a role in ANP depletion in ALAFers. We know that ANP is also a marker for salt sensitivity. Many ALAFers have mild hypertension. Their increased ANP would drive the increase in AT1s.

So, it would seem that increased left atrial AT1 receptors in LAF represent effect.

During an episode of AF atrial stretch related secretion of ANP and consequent sodium diuresis (the big pee) causes volume depletion triggering the RAS. The drop in cardiac output (due to the loss of atrial assistance) and its effect on the juxtaglomerular apparatus (baroreceptor) in the kidney provides additional stimulus to the RAS. Therefore, increased ANP translates to increased AT1 receptors in those with LAF (v. AF or NSR).

These AT1s then modify the cardiac substrate, making it more susceptible to AF (more shortening of the AERP). However, these AT1 receptors also lead to cardiac fibrosis and over time the cardiac substrate becomes even more receptive to AF (fibrosis induced dispersion). Unchecked inflammation (due to declining ANP and its anti-inflammatory properties) undoubtedly further fans the flames of fibrosis. AT1 receptors gradually decline in number, since there is less ANP to oppose. Fibrosis may well stimulate proliferation of AT2 receptors, which are considered cardioprotective.

Additionally it has been shown that increased intracellular calcium is intimately involved in the transition of AF from paroxysmal to permanent. ANP inhibits the L-type calcium channel (thereby lowering intracellular Ca⁺⁺) and ANPs gradual decline may herald longer, more frequent episodes on this basis.

Via the above mechanisms "AF begets AF".

If aldosterone can overcome ANP over time, then it may very well be capable of doing this during an episode. Since the predominant effect of the RAS is vagolytic, theoretically VMAF episode termination should then be accompanied by a drop in HRV and an increase in HR. I have observed this many times (Polar HR monitor) and such has been reported in the medical literature.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12875412&dopt=Abstract

The time distribution of AF episodes shows remarkable age dependence with a distinct circadian rhythm in those less than 60 and a toneless pattern in those over 60.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9856920&dopt=Abstract

AF due to structural heart disease age occurs later in life than does LAF. Perhaps without the autonomic (circadian) AERP shortening present in LAF more RAS induced substrate deterioration may be required for AF due to structural heart disease. This would certainly conform to the toneless pattern of episodes in those over 60.

LAF is probably more about shortening of the refractory period (neurohormonal) with relatively less dispersion of that refractoriness, whereas in AF (structural heart disease) there may be greater dispersion (due to fibrosis) with relatively less shortening of the AERP.

According to Hans' most recent survey on the topic (May 2003), 80% of LAFers are male. Other surveys (October

2004) have revealed a similar gender breakdown
<http://bmc.ub.uni-potsdam.de/1471-2261-4-13/>

Females with LAF are on average 6 years older than their male counterparts. This age differential is even more pronounced in AF due to structural heart disease.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9856920&dopt=Abstract

These gender differences within LAF/AF fit well with research findings on ANPs gender connection.

Nonetheless, P cells (or their equivalent) appear to be the critical link in all forms of AF. Without their presence it appears that AF cannot be triggered. In Sessions 35 and 37 of the CR and in the March issue of the AFIB Report the probable role of P cells in the initiation of AF was discussed. In addition to the evidence therein cited supporting that interpretation there has been additional research by the Cleveland Clinic (February 2005) showing that the cells in the PVs that trigger AF react to pharmacologic agents in a fashion similar to the SA node (P cells).

<http://www.blackwell-synergy.com/doi/abs/10.1046/j.1540-8167.2005.40333.x?journalCode=jce>

Two Taiwanese EP canine studies in 2002 revealed the presence of pacemaker type cells (?P cells) in the SVC and PVs.

<http://circ.ahajournals.org/cgi/content/abstract/105/22/2679>

<http://www.ijbem.org/volume4/number2/115.htm>

PVI is effective at terminating LAF/AF because it isolates triggering foci that are probably P cells. However, sometimes it is necessary to ablate foci other than the PVs. These other foci are located in sites such as the posterior left atrium, the right atrium, the coronary sinus, the SVC, crista terminalis and the ligament of Marshall. Sometimes AF triggering foci can even be located in the thoracic veins. As previously reported, P cells, normally only present in the SA and AV nodes, have recently been documented in the PVs of those with atrial fibrillation (v. controls). However, these other non PV triggering foci are pretty much located where one would predict P cells (neural crest cells) to be found based on their migration pattern during embryologic and fetal development (venous pole, sinus venosus, PVs).

<http://www3.interscience.wiley.com/cgi-bin/bookhome/104558278/>

At least one article suggests that tissue dilatation adjacent to these misplaced pacemaker cells is somehow involved in their activation.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15828887&query_hl=2

Perhaps the observed stretch of adjacent tissue enables reentry of P cell impulses. Could all LAF initially manifest as brief episodes of tachycardia? PV tachycardia has only recently been described. Like AF, supraventricular tachycardia (SVT) in general is also increasing in frequency.

Although PVI by an experienced operator is usually quite successful, left atrial scarring is a powerful independent indicator of PVI failure.

<http://content.onlinejacc.org/cgi/content/abstract/45/2/285>

AF induced fibrosis probably enables abnormal circuits to reestablish contact with the left atrium post ablation. The fact that aldosterone (RAS) causes cardiac fibrosis and ACEIs and ARBs appear to be more effective in preventing recurrent and new onset AF in those with structural heart disease (v. LAF) further supports this interpretation.

Philippe Coumel once wrote that we must always bear in mind the complexity of autonomic interactions and how cautious our AF hypotheses should be for they are simple compared to reality.

Hopefully the reader will apply all due caution in their evaluation of my hypotheses.

Conclusion

What does all this mean? IMHO P cells are probably present in much of the general population. One article found ectopic pacemaker type cells in 3 of 14 dogs. And they were only evaluating the left inferior PV and these dogs did not have AF.

<http://www.ijbem.org/volume4/number2/115.htm>

This suggests that AF may not primarily be a channelopathy (other than in the rare familial cases of AF). Perhaps P cells produce increased PACs but not AF until there is sufficient substrate modification (dilatation, fibrosis).

In Coumel's triangle of arrhythmogenesis autonomic factors only modulate AF. Triggers and defective substrate appear to be at the root of the problem. Anti-arrhythmic agents seem to primarily target autonomic modulation without definitively addressing either the triggers or deteriorating substrate. PVI effectively targets the former thereby also halting the latter.

Both of my parents and an uncle have/had AF but not until well into their 70's. Two died of associated ischemic strokes. None of them were endurance athletes at any point in their lives. Since for many years I was, perhaps AF might not have reared its ugly head until I was in my 70s had I been more sedentary.

There are a rare few that are able to avoid AF episodes by diet (esp. plenty of potassium) and behavior modification alone. IMHO usage of antiarrhythmics for LAF is ultimately only a delaying tactic, longer for some than for others. But at the end of the day those individuals will always be at risk for AF in the absence of a successful PVI.

PC v56

PC, "There are a rare few that are able to avoid AF episodes by diet (esp. plenty of potassium) and behavior modification alone." PC, I think we are less rare than it seems to you, but of course there are no hard figures to support this view, only subjective impressions. This glass appears half full to me, not half empty.

How do the GERD associated afibbers fit into this, and the sleep apnea ones, and the H.pylori infected?

PeggyM

In order to avoid information overload I deliberately avoided a detailed discussion of the origin of P cells. Indeed many might find the following pointless. Furthermore, how do P cells relate to hormones? It turns out that P cells may have several hormone connections to LAF.

In its earliest phase (less than one month) the heart is a peristaltic pump with an inflow (vein) and an outflow (artery). Septation does not occur until the second month of life. According to recent studies the cardiac conduction system comes from neural crest cells. These are cells that originate adjacent to the neural tube (primitive CNS). Those that eventually become the actual conduction system migrate into the heart via the arterial pole (eventual PA and aorta) and those that become the SA and AV nodes (P cells) migrate into the heart via the venous pole (eventual PVs and vena cavae). Incidentally P in "P cells" stands for pole and not for pacemaker. These SA and AV node P cells then become neurons complete with an autonomic connection to the rhombencephalon (primitive medulla).

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15248063

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10068463&dopt=Abstract

All CNS autonomic reflex connections to both sympathetic and parasympathetic nuclei are located in the medulla oblongata.

In Development of the Cardiac Conduction System (September 2003) <http://www3.interscience.wiley.com/cgi-bin/bookhome/104558278/>

it is stated that "during development there are sinoatrial tracts that run between the sinoatrial and the atrioventricular node as well as tracts surrounding the pulmonary veins and the coronary sinus".

"The atria of the mature heart have more than one origin. The trabeculated portions of the right and left atria are from the primitive atria, whereas the smooth-walled posterior portions of the left and right atria originate from the incorporation of venous blood vessels. The posterior aspect of the left atrium is formed by the incorporation of the pulmonary veins, whereas the posterior smooth portion of the right atrium is derived from the sinus venosus."

<http://pediatriccardiology.uchicago.edu/MP/CHD/ASD/asd.htm>

<http://cogprints.org/4182/>

The Ligament of Marshall is a venous remnant in the left atrium.

<http://circ.ahajournals.org/cgi/content/full/109/7/828>

So, it would appear that progenitor P cells complete with their autonomic connections to the primitive medulla migrate to a multitude of venous sites, some of which eventually form part of the atria that fuses with the primitive atria (trabeculated). It is most coincidental that these same sites appear to comprise virtually all of the described "hot spots" that are capable of triggering AF. A list of these foci includes posterior left atrium, the right atrium, the coronary sinus, the SVC, crista terminalis, the ligament of Marshall.

<http://circ.ahajournals.org/cgi/content/abstract/107/25/3176>

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12914614&dopt=Abstract

Cardiac tissue has even been identified in the thoracic veins and has its origin from sinus venosus.

<http://www.ijbem.org/volume4/number2/115.htm>

AF triggering foci have also been identified in thoracic veins.

http://www.blackwellpublishing.com/more_reviews.asp?ref=1405118881

So, why are these cells present in some but not in others? The particular cell type that is formed from neural crest cells is dependent upon its destination, i.e., area where the cell migrates as well as upon its origin, i.e., where along the neural tube the cell arises. This process is governed by transcription factors. They also initiate apoptosis or programmed cell death. Neural crest cells are especially prone to apoptosis. Persistence of these culprit P cells may be a failure of apoptosis. Furthermore, obliteration of P cells (or not, as the case may be) may not stop at birth but may be ongoing. For example, the coronary sinus, a particularly arrhythmogenic site,

<http://cogprints.org/4182/>

has a valve that is present in 138/143 newborn hearts, 140/143 preteens, 111/143 teens and 40/143 adults. Perhaps the hormones of puberty play a role in closure of this valve. Coronary sinus defects such as this are often associated with a persistent left superior vena cava (ligament of Marshall) and atrial septal defects (ASDs). A patent foramen ovale (PFO) is the most common atrial septal defect. <http://www.emedicine.com/ped/topic2493.htm>

You may recall that Carol Andrews and "Michael in Australia" were found to have PFO by transesophageal echocardiogram (TEE). Yesterday I had my preablation TEE to exclude the presence of spontaneous echo contrast (SEC), and a PFO was discovered. I picked up on this during the procedure, although consciously sedated. And they didn't even require a Valsalva maneuver from me to see it. Of course, I'm eagerly awaiting the report (fortunately no SEC). In a previous post by Doug Symonds an association between AF and PFO was reported.

<http://www.barnesjewish.org/groups/default.asp?NavID=1323>

Although this is pure speculation, could the the absence of certain hormones (? during puberty) permit persistence of ASDs and P cells? PFOs are quite common. Could they be even more common in LAFers?

This is not the only possible LAF hormone connection. P cells are probably a factor in triggering many tachyarrhythmias. We know that this stimulates release of ANP. Calcium and sodium accumulates inside cardiac cells within minutes of onset. ANP works to alleviate this problem (see last bullet under ANP). After 24 hours of increased intracellular calcium and sodium several potassium channels are upregulated, leading to further shortening of the AERP (electrical remodeling). There is also downregulation of these same L-type calcium channels with "loss of physiologic rate adaptation". Perhaps gradual depletion of ANP (and loss of inhibition of these L-type calcium channels) drives the electrical remodelling.

<http://dissertations.ub.rug.nl/FILES/faculties/medicine/1999/r.g.tieleman/c10.pdf>

p. 172 , 179

In fast paced dogs "long term adaptations to 42 days of atrial tachycardia could be mimicked by blocking the L-type calcium channels".

<http://dissertations.ub.rug.nl/FILES/faculties/medicine/1999/r.g.tieleman/c10.pdf> p. 178

Herein may lie the primary difference between LAF and AF (structural heart disease). In the former AF results from tachyarrhythmia induced ANP depletion with electrical remodelling (reversible) and in the latter AF results from fibrosis induced ANP depletion with structural remodelling (irreversible).

<http://www.a-fib.com/BostonA-FibSymposium2004.htm>

This whole approach to explaining AF brings up a very controversial issue. Is the genetic component of AF due to an ion channel/pump abnormality (specification model) or to a transcription problem (recruitment model) or both? The

former appears to be more popular at present. A very recent article by Dr Brugada (J Cardiovasc Electrophysiol. 2005; 16 (5): 553-556) entitled "Is Atrial Fibrillation a Genetic Disease?" (<http://www.medscape.com/viewarticle/504559>) doesn't even mention transcription. Anatomists and embryologists appear to favor transcription and clinicians appear to favor channelopathy. Clearly familial AF (rare) is primarily due to mutations that cause channelopathies.

The above recruitment model dependent upon transcription factors for explaining AF fits quite well with the prominent role played by the autonomic nervous system in the genesis of AF episodes (P cells are hard wired to the ANS).

Why is AF rarely seen in the young, if vagal tone is highest at this time? I've known since I was a kid that I've had increased ectopic beats. But AF was not diagnosed until age 51. This suggests to me that the P cells have not changed, but that the cardiac substrate has. It has become more receptive to sustaining AF triggered by these P cell induced PACs. There are several possible explanations. In addition to the mechanism of dilatation => reentry => tachycardia => ANP/RAS activity => substrate modification, our atria get bigger as we grow and we may be able to accommodate the critical mass of sufficient wavelets (6 or more) for sustaining AF. This may in part explain the male predominance of VMAF (males being slightly larger than females). Inflammation appears to be part of the program as well and may further alter the cardiac substrate. Participation in endurance sports increases the risk of AF by 8-10 times. Is this mediated by physiologic enlargement of the atria or by increasing vagal tone or by inducing inflammation? Basketball players but not football players seem to be at greater risk for AF. Both have relatively larger atria, but the former are undoubtedly more fit than the latter. Perhaps as this cardiac substrate becomes structurally abnormal with increasing age only then does LAF (average age at diagnosis of 50) rear its ugly head.

PC

"For example, the coronary sinus, a particularly arrhythmogenic site, <http://cogprints.org/4182/> has a valve that is present in 138/143 newborn hearts, 140/143 preteens, 111/143 teens and 40/143 adults. Perhaps the hormones of puberty play a role in closure of this valve. "

"Although this is pure speculation, could the absence of certain hormones (? during puberty) permit persistence of ASDs and P cells? PFOs are quite common. Could they be even more common in LAFers?"

A particularly interesting bit to me: I didn't go through puberty until I was well turned 16..... are there any other AFrs here who did not go through puberty until relatively late on??

Mike F.

(P.S. helluva post (x2) PC!)

Wow - this is all so helpful and informative PC. Thank you. I was particularly interested in this simple statement, being new to LAF and still trying to work a few things out! "(P cells are hard wired to the ANS)".

This is probably very basic information, but I am still learning about P cells and also I was still having difficulty trying to explain to my mother (who I am sure thinks I am exaggerating when I try to tell her how debilitating LAF is when it is occurring on a daily basis!) on the phone this morning why diet, the ANS and AF are all related. I would be much better able to explain it to her now. (My Dad apparently had AF from his 50s through until he died at 83. My Mum doesn't seem to be able to explain what medication he was on or what was done about it - he did have a stroke at age 78, (which left him depressed rather than disabled) until he died. He also had hypertension and an enlarged heart, so probably not LAF, though could have been originally without being diagnosed as such.) My sister, 49, already has permanent LAF and another sister has developed AF (52). I am 54.

Once again, thank you for your time and trouble,

Patsy

Aloha Patsy,

It is my extreme pleasure to be of service to you through Hans' wonderful website.

Good luck to you and your family.

You must be somewhat concerned about the future heart health of your children, if any. I know I am. I'm presently working on a prospective science fair project with my son that is a combination of survey and field work amongst those at risk v. controls. When I'm sufficiently satisfied with the survey part, Hans has graciously consented to allow me to test it out in the CR and perhaps tweak it a bit. So stay tuned.

PC

P.S. Thank you for taking the time to read my posts and commenting on them.

It appears that this boiling cauldron of discussion needs additional spice. Actually my goal is to produce the first Session in the CR in which posts from the originator exceed all others. Also, better that you have information overload than calcium overload.

Up to now I have only implicated AT1s in the ANP/RAS program. I have also mentioned the possible role of apoptosis in P cells. There has been additional research implicating AT1s with apoptosis of nodal cells.

Angiotensin II May Mediate Apoptosis Via AT1-Receptors In The Rat Cardiac Conduction System.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15526249&query_hl=4

It basically states that there may be a correlation between Ang II (via AT1s) and apoptosis (increased) in the SA node, which does not appear to be present in the AV node (decreased).

Could LAFers with their increased AT1s have decreased apoptosis of ectopic P cells (v. the SA node)?

In addition to AngII the hormones of puberty and cortisol are potent generators of apoptosis.

PC

I'm going to post on the normal board & the current CR topic.

In this CR, PC says, "There are a rare few that are able to avoid AF episodes by diet (esp. plenty of potassium) and behavior modification alone. IMHO usage of antiarrhythmics for LAF is ultimately only a delaying tactic, longer for some than for others. But at the end of the day those individuals will always be at risk for AF in the absence of a successful PVI."

This study may indicate why. Incoming AF patients were separated into groups that had low serum Mg or K or both levels and those who were normal in both. 22% were low in one or both Mg or K. Both of these groups received an infusion of Mg, K, insulin and glucose. This infusion converted 86% of the low electrolyte group, but only 39% of the normal electrolyte group.

My hypothesis is that those in the low electrolyte group (22%) would benefit the most from supplements & diet.

PC - sorry to add a post, which means the originator will have more work to do.

George

Article is here:

<http://www.kardiologiapolska.pl/archiwum.php?vol=60&iss=6&pg=578&lang=en>

Polish Heart Journal, June 2004, Vol. 60, No. 6

Jacek Cybulski, Andrzej Budaj, Henryk Danielewicz, Janusz Maciejewicz, Leszek Ceremuski

A new-onset atrial fibrillation: the incidence of potassium and magnesium deficiency. The efficacy of intravenous potassium / magnesium supplementation in cardioversion to sinus rhythm

Klinika Kardiologii CMKP, Szpital Grochowski, Warszawa, Poland

METHODS

The study was primarily designed to assess the safety and efficacy of intravenous amiodarone in pharmacological cardioversion in a randomised trial, which was published elsewhere (5). One hundred and fifteen consecutive patients (71 men and 44 women; mean age 60.31±2.7 years) with a new-onset AF lasting less than 24 hours were included. AF was confirmed by a 12-lead electrocardiogram in all patients. Only the patients with a well-defined onset of arrhythmia were considered eligible. The time limit was set up to avoid prolonged anticoagulation therapy, which is necessary before cardioversion of AF lasting more than 48 hours. The study treatment was therefore designed not to exceed 20 hours leaving at least 4 hours for alternative methods of cardioversion, which were left to the discretion of the attending physician.

After screening for inclusion/exclusion criteria and written informed consent was obtained, the patients with electrolyte imbalance (serum K level <3.5 mmol/l or/and serum Mg level <1.7 mg/dl) received an infusion of 1000 ml of 10% glucose with 10 IU of rapid action insulin, 80 mEq of potassium chloride and 8.0 g of magnesium sulphate (GIKM) in open fashion (study group 1). Patients with K/Mg serum levels within normal range (study group 2) were randomly assigned to the two groups receiving GIKM alone (study group 2a) or with amiodarone (study group 2b) in 1:2 fashion. In this study, the efficacy of K/Mg supplementation was compared only between the two groups receiving GIKM alone (group 1 vs group 2a).

Study treatment was administered through either the peripheral or the central vein and maintained up to 20 hours independent of sinus rhythm restoration.

The Local Ethics Committee approved study the protocol and written informed consent was obtained from each patient prior to study entry.

RESULTS

Among the 115 patients with AF on admission, 22 (19%) had K and/or Mg level below the lower limit of normal range. Hypomagnesemia was found in 18 patients and hypokalemia in 4 patients with AF. Only one patient had lowered serum levels of both electrolytes. Patients in group 1 were significantly more frequent on concomitant treatment with diuretics, compared with patients without K/Mg deficiency (41 vs 18%, $p=0.04$).

Twenty hours after initiation of therapy, sinus rhythm was restored in 19 patients in group 1 and in 12 patients in control group 2a (86 vs 39%, $p<0.001$).

By the way, my own serum potassium was 3.2 mmol/l when I went to the ER for my first afib episode, so I was clearly in the low electrolyte group. Serum Mg was not measured at that time, but it was not low previously or since (I know, serum Mg is not a good measure for cellular Mg).

George

How do you follow this stuff? It more than gives me a brain cramp just skimming it.

Right now, afib is the main focus point of my life. It is messing up my sleep patterns, because I am afraid to lay down and I end up checking my pulse several times during the night. And that's during the nights I'm not fibbing!

My computer was down at home over the weekend, due to some remodeling we had done, so I am spending most of my morning today at work trying to find solutions or just an approach. Suffice it to say, I am a bit depressed over this right now.

Having engaged, and still engaging in, endurance type sports, I believe the increased vagal tone is at play. I do have a mildly enlarged atrium, although the report said it was consistent with an active life style.

I don't even try to understand the chemistry. But something, sometimes, seems to make my heart slow down a little more than usual and then I get "flutters". The flutters can turn into afib, or I can walk around and usually make them go away.

I also believe the potassium issue is much more critical than the doctors allow. We need some simple way to find out if it is a cellular problem for us, and if so, how to monitor and change it.

Actually, I think made exactly 0 contribution to this forum!

John

John,

I'm vagal & have been chronically fit my entire adult life. Before I corrected my electrolyte issues, I had early morning afib episodes, and also had triggers from eating junk late.

The results of this program of correcting my electrolyte deficiencies on my afib "load" i.e. the % of time spent in afib is as follows: before, 1860 hours out of 3240 hours (my 1st 4.5 months of diagnosis) or 57%, after adoption, 20 hours out of 5760 hours (my next 8 months of diagnosis) or 0.3%. And actually, in the last 7 months it has been 1 hour out of 5040 hours or 0.02%.

I monitor my ectopic count and can see the effect of emotions (fear, anger, stress) and hard exercise on my level of ectopics. Also, my triggers no longer seem to matter. My normal supplement program is: (2x day) of 1.5 grams K as citrate, 2 grams Taurine, 2 grams Acetyl L- Carnitine and 0.4 grams Mg as glycinate. This corrects the increased ectopic count quickly (within a couple of hours). It would be even more optimal to divide the dosage in half and take it 4x/day. However this 2x/day schedule works well enough.

My heart rate is as vagal as ever, and can drop to the low 40's during sleep or meditation. This is not an issue now that my tissues have sufficient electrolytes.

This may not work for everyone, but, if low electrolytes are your issue, it might help.

George

This link doesn't always work:

<http://www.kardiologiapolska.pl/archieve.php?vol=60&iss=6&pg=578> =en

So to get to the full article, you must:

- 1) click on "English Version" (unless you read Polish)
 - 2) click on "Archive"
 - 3) choose June 2004
 - 4) click on the article on p 578
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Hi Hans and PC,

I have posted my latest natto observations for discussion under this topic. If what I am experiencing with natto is not hormonal then I don't know what is!

Natto food 3 months on – My “new “ heart.

I have religiously been eating my 50 gm natto on a daily basis for nearly 3 months and the last 4 weeks have seen significant developments. I have categorised the observations below:

Heart

I have been afib free for 2yrs and 4 mths but in that time I have still suffered from bad ectopics, SVT (tachycardia), and at times, raised blood pressure. Since starting the natto food 3 mths ago my heart has gradually quietened itself to the stage that over the last 4 weeks I have been nearly totally ectopic and tachy. free, maybe one or two noticeable pac's every 2nd or 3rd day. The best way to describe the beating of my heart would be to compare it with taking strong beta blockers – a very steady, quiet beat, so quiet in fact that I sometimes feel my pulse just to make sure.....I no longer have a strong thumping heart beat and ectopics that suddenly start for no reason. When I used to get ectopics I would make them worse because of my fear of afib by an adrenaline “hit” at the same time. This adrenaline surge with ectopics has now disappeared completely.

Over the last 3 weeks I have been deliberately trying to induce ectopics and tachy. – eating large meals, going to bed early and sleeping on left side, consuming excess alcohol (great fun) etc. I just can't induce ectopics anymore. It's as if (dare I even think it?) my arrhythmia problems have gone.

Blood Viscosity

Blood more watery and a very bright red/pink colour. Not the deep dark red it used to be. When I started natto, blood would pour out of a wound but now the opposite.

Stamina

Just as all the Japanese literature on natto has stated, I have about a 10 to 15% increase in overall stamina. This is particularly noticeable when I'm playing golf on my local very hilly golf course. It takes a real good physical effort before my pulse rate rises and my breathing quickens. I can easily keep up with my playing partners who are in their late 20's.

Kidneys

Gradual and now very noticeable increase in urination over last 3 months. Larger volume and increased diameter of urine stream.

Fingernails, toenails, hair

The strongest indication that natto is working is in the fast growth of my fingernails and to a lesser extent, my toenails and hair. Fingernails are also much tougher and do not split or delaminate.

Back and other aches and pains

Haven't heard a peep out of my dodgy back and other niggling aches (old sporting injuries) in joints have disappeared.

Stress

A definite decrease in stress levels probably due to the fact my adrenaline has decreased. Great for stressful business meetings.

Decreased libido

The only “downside” of natto so far. I think I covered this matter in depth in a previous post so won't comment and embarrass Jackie any further.

Digestive system

Much quieter digestive system all around. Hardly any stomach upsets and stools just about perfect.

Weight loss

Have lost about 3kg – probably due to water loss due to increased kidney function?

My observations overall

The most noticeable change since starting natto is one of decrease adrenaline production. The 10 to 12% reduction in blood pressure that natto literature states must be kicking in. This maybe behind decrease in libido too. Due to the increase in urine there must be some sort of change in my kidneys and adrenal glands. The increase in diameter of the urine stream suggests a shrinking of the prostate. Natto is suppose to help prostate as well – maybe something to do with libido too.

The extra stamina has to be coming from increased micro circulation and reduction in calcification (I have not varied my exercise routine at all) I have made a point of not varying my normal diet since starting natto. I do not take any supplements – the only drug being 20mg Losec daily for reflux. I avoid any foods high in sugar (no chocolate for 2 and half yrs) and eat plenty of green vegetables. My big diet sin is alcohol – beer and red wine.

Overall, the biggest effect must be the scavenging of calcium by the Gla protein natto stimulates:

“Vitamin K works through an amino acid called "Gla," which stands for gamma-carboxyglutamic acid. Gla is a part of the kind of protein that controls calcium. Vitamin K is necessary for this protein to do it's work. Vitamin K performs this feat by "carboxylation" which gives proteins the adhesion they need to hold onto calcium. The proteins then move the calcium around. If proteins don't get enough vitamin K, they can't maintain the adhesion needed to move the calcium and the calcium will drift out of the bones and into the arteries and other soft tissues. (Gordon)”

As I am not a suitable candidate for ablation my only option is to search for the “holy grail”, that is, heart remodelling. From the above observations I am keeping my fingers crossed that this natto muck is taking me there.

Looking forward to everybody's comments and suggestions.

Dean

Mike,

Great question to ask.

Same as you, puberty late 16. Was always told by doctors, school teachers etc. that I was "underdeveloped". This was a constant theme in my teens. Even now, although I am 49, people who don't know me think I am in my 30's. I remember Fran saying the same thing on numerous occasions that she looked far younger than she was. Maybe at each stage of our development our genes switch off a fraction too soon - like trapping P cells before they reach their assigned place.

Are afibbers slightly underdeveloped humans? A very mild form of Aspergers?

Dean

Hi Mike, Dean, Hans & PC,

I'm not sure that I was a late bloomer (mentally, maybe, but not physically) with puberty at 14 or so.

As to Natto, I started measuring my blood glucose in February. By modifying my eating pattern to keep blood sugar from spiking, I lost 20 pounds (~9 kg) over two months. I originally wanted to see if I had blood sugar issues that might be an afib trigger. This was not the case.

I found that I could control my fasting glucose by what I ate the day before. If I stuck to my low fat vegan diet, my fasting glucose would be in the 80's. If I added a bunch of fat to the same meal, I could spike it to >110.

I've been eating Natto for about 3 weeks now (50 grams/day). I was going to wait a bit before I reported this, however now seems appropriate with Dean's post. I am much less strict with my diet and still get a low fasting glucose. The only change in my lifestyle is the Natto. I presume it is helping get excess calcium out of my cells. This is an issue for glucose intolerance and I documented it in myself with an EXATEST cellular mineral test last October.

After a few more months, I may repeat the EXATEST & see if the calcium results are different. Judging from Dean's post, I would expect they would be. This would then effect insulin's ability to process glucose (tying a hormone to this post).

George

I was also a late developer and did not get a normal cycle until I was 18. I think it was due to subclinical hypothyroidism. Also, after reviewing my medical records from over the years, I found that my potassium levels were always at the very bottom of the normal range. I seem to fit the group that would benefit from these minerals.

All this material is very interesting and helps me see how my A-fib is probably a culmination of many things happening over my lifetime.

I am impressed with stories about Natto.

Tish

I have posted a while back that I believe my afib is related to my hormones. I have mentioned this to a number of doctors but none seem to want to pursue this. I do have an article that I purchased for 25 dollars from Current Women's Health Report It was written by doctors and the title is The Effects of Hormones on Arrhythmias in Women. It states a definite connection. I had skipped beats at the beginning of each pregnancy and supraventricular tachycardia shortly after the birth of my first child. Over the years, I continued the episodes and at the time of menopause my heart started to skip beats daily. It still does. I had my first afib in January 2000. I have had more and more. I am on Rhythmol SR 325 2 times a day and Toprol XL 25 mg once a day/ Any help? I will share this article, but it is copyrighted. If you want to contact the periodical directly, please let me know.

Thanks,
Lynda

Dear Lynda,

Please share the article with me. I had no symptoms of problems until I just recently began menopause and every time I have a hot flash, my heart races or is uneven for a few seconds, now. I feel a definite connection of A-fib to my hormone status.

Tish

Tish and Lynda,

Perhaps this is the article to which you are referring in its entirety.

<http://www.biomedcentral.com/content/pdf/cr-wr2211.pdf>

PC
