THE AFIB REPORT
Your Premier Information Resource for Lone Atrial Fibrillation
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VIRTUAL LAF CONFERENCE

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SUBJECT: Mechanism of LAF

I received the following letter from Dieter a fellow afibber who raises a host of very interesting questions which may benefit from a thorough discussion here.

"I have been battling with LAF – both physically and mentally. I received your book a few months ago, and as you so aptly pointed out, trying to at least alleviate AF is very much a DIY affair. I have spent a lot of time, first studying your book, then searching the Internet, and of course thinking about the information I found.

I would very much appreciate receiving your comments on the thoughts that follow.

First, I must confess that I am not comfortable with the idea that an imbalance in the ANS should be the primary suspect in the mystery that is AF. Certainly, the hypothalamus / pituitary – ANS – endocrine system ('Control Centre') must be part of the picture. What puzzles me, though, is the fact that a very large variety of 'triggers' – all supposed to act through the ANS on the heart to cause AF – has been named. (I am not quite sure that coincidence has not perhaps played some role in pinning the 'trigger' label on some or other item in the long list – this would be quite understandable if one is desperate to identify a cause–effect connection.) In addition one wonders why any imbalance in the ANS should manifest only in the heart and not anywhere else in the body – after all, the Control Centre has to handle many more bodily functions than just those that affect the heart.

My puzzlement concerns the undeniable fact that different 'triggers' will set in motion different responses in and from the Control Centre. Acute stress differs in this respect from persistent stress, physical exertion is different again, all three differ from the response produced by stimulants, etc. There is simply no common thread discernible in such a multitude of distinct responses in the body. On top of that we have recorded instances where a mere cough or burp or some change in bodily position – all of which should generate a minimal Control Centre response – can apparently provoke an AF episode.

Attempts to influence the ANS – to correct an assumed imbalance – through dietary restrictions, supplements, medication have met with only very limited success. Nothing proposed so far has come close to a cure. All we have is some help in some cases – reduction of episode frequency and/or intensity, perhaps (but only perhaps) a shortening of episode duration, and this often only for a limited time.

I believe that the area of investigation into the possible causes of AF should be widened. Before I tell you what I have in mind, there are some questions on which I need your help:

Descriptions of what produces AF generally say that the normal function of the SA node is drowned out by the action of circular electrical activity ('wavelets') that wander throughout the atria. These spinning wavelets generate discharges at a rate of 300 – 350 / minute, possibly even faster. Since the contractile tissue in the atria will always follow the fastest

frequency, the SA node with its inherent beat of 60 – 80 / minute stands no chance. What sets off the activity of these wavelets, and what makes it stop (in paroxysmal LAF), remains unexplained, or should I say: unknown. But: Do the active wavelets follow the rule that 'the fastest horse wins'? Or does this rule apply only to contractile tissue but not to pacemaker foci whose discharge rates can then differ from wavelet to wavelet?

Here are further questions: Why is the discharge rate of the wavelets so high? How is this frequency generated? Do the cells involved have a charge/discharge mechanism that differs from that of the cells in the SA node? What is their action potential? Does the action of the SA node continue during an AF episode, or is there perhaps any change in its impulse generating mechanism?

When the heart is beating normally, i.e. in NSR, each impulse travels from the SA node throughout the right atrium into the left atrium and down, through the AV node, into the ventricles. This seems to be essentially a straight-line propagation, each cell passing on the 'contract!' instruction to its next neighbour. It is, however, not clear to me how wandering islets of circular currents who are active within a circumscribed area or space can affect all contractile tissue in both atria. I understand from what I have read that a minimum of six such wavelets is required before AF sets in. What is the significance of this threshold? What is the size of the wavelets in relation to the atria? How can circular currents, limited in space, influence the entire atria volume? When does a wavelet contribute to the impulse frequency that the AV node has to contend with? If wavelets travel well within the atria without getting close to the AV node, and do not generate pulses that travel throughout the atria, surely they will not have any influence on the AV node at all?

And another what-if: If six ectopics set off an episode, and five don't – would that not be a hairtrigger situation, with very little required to push matters over the edge? Could that perhaps explain why some, in normal circumstances, trivial things can have a major effect on the heart and trigger an AF episode?

I have also read that wavelets that meet head-on will annihilate each other. Does that mean that the number of wavelets diminishes and that they will eventually disappear completely? This might be a mechanism to explain the spontaneous termination of AF episodes. Or will fresh wavelets be generated throughout an episode in progress?

My understanding is that the wavelets that cause AF originate in ectopic sites. I feel reluctant to view the existence of such sites as something abnormal. Consider the fact – as reported by yourself – that 60% of adults experience ectopic beats, at least from time to time. Such widespread occurrence points to my mind to a normal state of affairs, i.e. that ectopic sites are a standard feature of the heart. Perhaps all the other people who have not had any ectopic beats, do possess ectopic sites that are merely dormant…? Moreover, ectopic pacemakers can take over should the SA node fail for any reason. The problem with AF is, though, that several sites spring into action at the same time, and do so at a frequency too fast for comfort. That needs explanation.

Has there ever been a close examination of such ectopic sites to determine whether they differ structurally or, when everything works normally, in functionality from any other cells in the atria? In this context, here is a quote from one of the internet sources I found: 'Ectopic foci in the atria, near where the SA Node is located, pace anywhere from 60-80 beats per minute – similar to the SA Node. Ectopic foci located farther away from the SA Node pace much more slowly. Those in the AV Junction pace anywhere from 40-60 beats per minute, while those in the ventricles pace from 20-40 beats per minute.' Where does this very high rate of 300-350 b.p.m. in AF episodes come from?

By now the thrust of my thinking is probably apparent to you: I believe that the cause of AF is within the heart itself, although the Control Centre will of course be involved and contribute to the initiation of episodes. I have an idea, however, that one should look much more closely at the SA node to determine whether changes in its capacity to follow instructions from the Control Centre, and to generate impulses, are present in Afibbers, and whether such changes are age- or disease-related. Here is one scenario:

The heart does not simply await instructions from the SA node. I believe it is very much aware, through nerves and through the blood coursing through it, of what is happening elsewhere in the body. Remember those reports where recipients of donor hearts suddenly developed a taste for food they disdained previously? The heart remembered….! Would it then be surprising if the heart became aware of a need to pump faster at about the same time such directive were issued by the Control Centre? It would not surprise me. But what happens if the SA node fails to respond, or respond quickly enough, to an order for faster pumping action? Or if the impulses delivered to the atria are too feeble? Is it not thinkable that the heart will then use fall-back pacemakers, i.e. the ectopic sites mentioned earlier on?

My tentative feeling is that one's SA node might become enfeebled with advancing age, or have suffered some damage over the years. It would be reasonable to assume that the SA node's pacemaker capacity might have become compromised to some extent and fail to 'deliver the goods', if not permanently (as in permanent AF….), then perhaps for periods of time (as in paroxysmal AF). Apart from the SA node itself, there might also be some defect in the electrical conduction system of the heart. The progression from paroxysmal to persistent to permanent AF could be explained if one finds that the originally sound heart develops first an intermittent fault (in the SA node and its associated electrical conduction system) which then gradually becomes more pronounced and finally – well – permanent. Does that make any sense?

Finally this question: In AF we are dealing with an electric phenomenon. Have you in your wide-ranging searches come across any report that magnetic-field therapy has been shown to be of benefit to afibbers?"

Dieter

Dieter,

Thank you for your most interesting letter! I have a few comments:

1. I don't believe there is any question that the autonomic nervous system is involved in afib initiation. Numerous studies have shown a marked shift in ANS balance just prior to initiation.

2. I don't believe the specific triggers are coincidental. When 61 of 133 afibbers mention emotional stress and anxiety and 43 mention alcoholic drinks as triggers, this has to be more than mere coincidence.

3. I agree that attempts to influence the ANS so as to prevent afib have been largely unsuccessful. I believe we need to correct abnormalities in the heart tissue as such.

4. I am not all that familiar with wavelet and related theories, but know of several Conference Room contributors who are. Perhaps we will hear from them?

5. You are correct that ectopic sites and ectopic beats are quite common. I believe what set afibbers apart is that they experience many more (10-100 times more on a "bad" day).

6. I have not come across any data indicating that magnetic field therapy may be beneficial in afib. However, there is some indication that EMFs can trigger afib under certain circumstances.

Hans

Hello Hans

What do you mean by #3 - "attempts to influence the ANS so as to prevent Afib have been largely unsuccessful." Are you referring to treatment by drugs?

Carol

Carol,

I was actually thinking more of diet and supplements, but I guess the statement applies to medicines as well. I am not aware of any therapy that has been able to successfully prevent afib episodes through their action on the autonomic nervous system.

Hans

I am one of those who believe that an imbalance in the ANS mediated by an imbalance in the endocrine system is the primary cause of AF in many people (self included). Remodelling might well lead to a greater propensity over time.
My reasons for believing this are:
1. A chart of my AF episodes over a year shows a dramatically clear sine wave over 24 hours with maximum AF incidence at 19:00 and a minimum 12 hours earlier (Hans has a copy). What else in the body shows this sort of pattern than the endocrine system?
2. I have vagal AF which reached a frequency of once or twice a week for an average of 9 hours each time. Since starting Disopyramide 15 months ago, I have had no AF worth talking about (a few minutes on two occasions). I believe that this is because of the vagalytic effect of this drug (Atropine) rather than its effect on the QT interval.
3. Towards the top of the sine curve (afternoons and evenings), a number of triggers have started AF episodes including: Bending, belching (pardon!), eating and drinking or sometimes nothing at all. In other words, when I am sensitive, any one of a number of triggers can set off AF, Interesting though that they can all be linked with the gut one way or another including posture.

I still think that a 6 hourly saliva test for key endocrine elements on a number of vagal volunteers might show a common pattern or at least knock this idea on the head and let us get on with other things.

Ever thought of organising such a trial Hans if volunteers paid their own costs. There would need to be a common protocol.

Bill

Bill,

The endocrine system does show the pattern you mentioned. It is interesting that testosterone level peaks at about 7:00 am give or take an hour and then starts down.

John S.

Bill,

My own AF is starting to show a pattern of kicking off at 3 am and self-converting (no meds) about 3-4 hrs later. Is an ASP (adrenocortex stress profile - to measure cortisol and DHEA) test one of the tests to which you are referring? I KNOW I can at least get that done here in the UK (for £70-00 - see http://www.drmyhill.co.uk/test.cfm?id=55). If a survey is undertaken, count me in..... at least for as many tests as I can get here in the UK. More info can only help.

Mike F.

Dear Bill,

Hormone levels are not the only physiologic parameter that can follow a diurnal pattern. Vagal tone is so disposed and involves no circulating or measurable hormones.

Regarding vagal tone and the QT interval, see my post of 11/3 and the web link Richard provided
http://clapham.tch.harvard.edu/researchtopic.html?subject=girks

Here again, a potassium channel, specifically IKACh is responsible for any change in vagal tone.
The article I cited earlier under this topic further underscores this association (in mice).

I too have experienced a remarkable improvement in my LAF since commencing disopyramide and experimentally tweaking its dosages and timing regimen.

It is precisely because of an experience similar to yours that I believe that IKACh is the primary problem. This is the best way to attack LAF wrt a pharmaceutical approach.

The problem with disopyramide is that it is indiscriminate wrt muscarinic receptor sites. It sure would be nice to find one that specifically targets M2 receptors.

All these GI related and position related triggers in my opinion probably do this via an innocent bystander effect. I posted the specifics of how I think this works on the BB on 3/9/02 wrt swallowing triggering an episode. Please visit http://www.afibbers.org/forum/read.php?f=2&i=9806&t=9806

Most people with GERD do not have LAF. GI related functions in the vast majority of humankind do not trigger LAF. Some nonGI related diseases that have a strong association with LAF (>10%) are hyperthyroidism and hypokalemic periodic paralysis. Here again the final common pathway is probably a potassium channel. At no point for such individuals is the GI tract involved.

Adrenergic LAF may be linked to some ion channelopathy causing AF via stress related free radical or aldosterone mediated cardiac cell membrane damage.

This is just my opinion and is not meant as a challenge to yours, only to stimulate input from others.

Bill, are you or were you at one time an endurance athlete?

PC v54

There are many excellent pages and links to articles at:

http://www.clevelandclinic.org

This page in particular, "Innovations: Research in Atrial Fibrillation", is quite interesting as it provides clear descriptions and illustrations re: mechanisms of AF:

http://www.clevelandclinic.org/heartcenter/pub/atrial_fibrillation/AFresearch.htm

Erling

I throw this out to all of you excellent contributors who have a background in science/physiology. I was doing a little reading on the net about the problem for pregnant women of uterine irritability which causes premature contractions which can lead to pre-term delivery. Seems that prostaglandins are at the root of this, and treatment involves magnesium sulphate, terbutaline and other therapies that somehow cancel out the effect of prostaglandins on smooth muscle contraction. I was interested because my daughter has had this problem, and then I looked at a few sites that explain the role of prostaglandins in the heart muscle tissue. Seems that this tissue hormone is involved in sodium, potassium, calcium crossing the cell membrane and thus triggering contraction. Could it have a role in making heart muscle cells overly excitable, setting the stage for a-fib?

Anyway, I'd be interested if any of you find this an area of possible exploration.

Mary

Mary

I don't have a background in science or physiology, but I found your connection interesting. When pregnant (all three times) I have had a history of early contractions and false labour. Also AF started after the 1st pregnancy and was a lot worse throughout my two other pregnancies all with 18 to 20 hour labour and terrible contractions for weeks following labour. I will have to search on prostaglandins.

Thanks

Fran

Mary

I am the one who stopped AF through eliminating free glutamate from my diet. After you post about prostaglandins which really rung a bell for me. I did a search on prostaglandins and glutamate....

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?holding=npg&cmd=Retrieve&db=PubMed&list_uids=9440691&dopt=Abstract

Nature. 1998 Jan 15;391(6664):281-5. Related Articles, Links

Prostaglandins stimulate calcium-dependent glutamate release in astrocytes.

Bezzi P, Carmignoto G, Pasti L, Vesce S, Rossi D, Rizzini BL, Pozzan T, Volterra A.
Institute of Pharmacological Sciences, University of Milan, Italy.

Astrocytes in the brain form an intimately associated network with neurons. They respond to neuronal activity and synaptically released glutamate by raising intracellular calcium concentration ([Ca2+]i), which could represent the start of back-signalling to neurons. Here we show that coactivation of the AMPA/kainate and metabotropic glutamate receptors (mGluRs) on astrocytes stimulates these cells to release glutamate through a Ca2+-dependent process mediated by prostaglandins. Pharmacological inhibition of prostaglandin synthesis prevents glutamate release, whereas application of prostaglandins (in particular PGE2) mimics and occludes the releasing action of GluR agonists. PGE2 promotes Ca2+-dependent glutamate release from cultured astrocytes and also from acute brain slices under conditions that suppress neuronal exocytotic release. When applied to the CA1 hippocampal region, PGE2 induces increases in [Ca2+]i both in astrocytes and in neurons. The [Ca2+]i increase in neurons is mediated by glutamate released from astrocytes, because it is abolished by GluR antagonists. Our results reveal a new pathway of regulated transmitter release from astrocytes and outline the existence of an integrated glutamatergic cross-talk between neurons and astrocytes in situ that may play critical roles in synaptic plasticity and in neurotoxicity.

I'm thinking this may be the link I have been looking for. But this to me would suggest that AF did not originate in the heart tissue - but will change it over time.

Fran

Finally a topic to which I'm more suited.

Dieter has asked some interesting questions. Obviously he has been doing a great deal of thinking about our little unwelcome visitor.

Dieter's questions are predominantly within the realm of electrophysiology. I think I can answer some of them or at least provide a better understanding of what is probably happening in the heart. Many of you have previously seen my post on this. I've tried to expand upon it somewhat.

First of all, one should not confuse wavelets with PACs. The former only exist during AF. The latter, as has been

suggested, are a completely normal phenomenon, but are decidedly increased in LAFers.

The frequency of PAC pairs (consecutive PACs) is inversely proportional to the time interval before the next episode of AF. It is the trigger that initiates AF. PACs for the vast majority of LAFers, most frequently originate in the left atrial tissue near the pulmonary vein ostia. These cardiac cells are higher in the atrium and closer to the SA node and hence have a higher innate rate of firing (automaticity). As described by Hans on pp. 137-138 of his book, these cells are more likely than any other heart cells to be damaged by oxidative stress from reactive oxygen species (ROS) coming from the lungs. This must be accelerated in endurance athletes. Postop AF after major surgery occurs via the same mechanism and is called ischemia reperfusion injury. Although some (www.lammd.com) feel that the cellular damage that causes AF is probably mitochondrial, I think that it makes much more sense to ascribe this to lipid peroxidation of the cell membrane (see post on BB). After all this is where the ion channelopathies are born. And ion channels are what determine action potentials, refractory periods, etc. They are under the direct control of vagal nerve fibers (present in the heart only in the atria) through M2 muscarinic receptors. Sympathetic nerve fibers also play a role through adrenergic receptor sites in both the atria and ventricles. As Dieter intimated, aging causes damage to the heart both via oxidative stress and hormonal receptor mediated fibrosis. The former is probably more prominent in vagal LAFers and the latter is probably more prominent in adrenergic LAFers, but there is undoubtedly considerable overlap. When these target the SA node with loss of its automaticity, it's called Sick Sinus Syndrome.

Progressive damage to these ion channels can result in "loss of physiologic rate adaptation". Adrenergic LAFers have an inappropriate shortening of the atrial effective refractory period (AERP) at higher heart rates and vagal LAFers have a similar problem at lower heart rates. This problem and the increased PACs are probably related to ion channel damage.

The contractions initiated by PACs can impact those initiated by the SA node (NSR) in several different ways. I'm not a cardiologist, so bear with me. This is meant to address some of the questions raised by Dieter. Please excuse any excess technicality. R-R interval is the time in milliseconds between consecutive R waves (in the QRS complex on the EKG). Depending on when in the cycle the PAC occurs, it can 1) reset the SA node via its retrograde wave (the first R-R interval is shorter, followed by one that is of normal length); 2) block the signal or wave of contraction from the SA node, if this occurs during the refractory period after the PAC (the first R-R interval is shorter, followed by one that is longer before returning to normal length); 3) reset the SA node but result in a nonconducted wave, if the PAC is timed such that the anterograde wave encounters refractory tissue from the immediately preceding normal beat, but the retrograde wave does not (the first R-R interval is longer, followed by one that is of normal length before returning to normal); 4) Consecutive PACs (1+3) can result in a shorter R-R interval followed by a longer one before returning to normal. This covers all four combinations of consecutive R-R intervals – long then normal, long then short then normal, short then normal, short then long then normal.

Muscle cells (skeletal, smooth and cardiac) contract during depolarization (excitation phase) and relax during repolarization. During a portion of the relaxation phase, the cell is refractory to further stimulation (refractory period). AF requires a AERP, enhanced atrial dispersion of refractoriness, slow cardiac conduction velocity and a trigger (increased PACs). Dispersion of refractoriness is nothing more than a measure of how much variability in AERP exists between adjacent atrial muscle cells. Greater variability in AERP from cell to cell implies greater dispersion.

The mechanism of AF is based on the now proven Moe wavelet theory (1959), which requires both reentry and automaticity. Reentry occurs when the advancing wavefront of depolarization (and contraction) encounters refractory tissue in such a way that it reenters its own path, creating a wavelet (circular wave). The lack of AERP uniformity between cells can force some unusual paths of conduction (colorfully called circus movements), making creation of these wavelets or closed circuits a real possibility. Wavelets are described by the equation:

wavelength = (conduction velocity) x (AERP).

Atrial conduction velocity (via normal pathway) is about 1m/s and AERP<50 ms results in AF 80% of the time. Plugging these values into the above equation suggests that a microreentrant wavelet (of Moe) is somewhere around 5 mm in circumference.

In addition to reentry, there must be automaticity, whereby a single atrial focus fires repeatedly (PACs). The number of PACs is inversely proportional to intracellular K and Mg and directly proportional to intracellular Ca. The SA and AV

nodes and the rest of the His Purkinje conduction system have innate pacemaking properties (automaticity). Catecholamines can cause automaticity in cells not so disposed (foci of ectopics). Since PACs arise outside the normal conduction system of the heart, the impulse travels via an alternate less efficient pathway with slower conduction velocity. This further contributes to shortening of the wavelength and dispersion of refractoriness (see above equation). The dispersion of refractoriness for adrenergics is probably due to cardiac fibrosis (possibly aldosterone mediated). Increased vagal tone causes not only shortening of the AERP but also increased dispersion of refractoriness. Inhomogeneous distribution of vagal nerve endings will increase dispersion of refractoriness. In vagal LAFers this latter may be in part due to the genetically determined three dimensional “fingerprint” of vagal nerve fibers in the atria.

These simultaneously occurring conditions (PACs, slow velocity, shortened AERP and enhanced dispersion) lead to AF by fragmentation of the propagating wavefront of depolarization. Multiple reentrant wavelets (six wavelets or involvement of about 75% of atrial tissue constitute critical mass for sustaining AF) are created. The dispersion of refractoriness allows the wavelets to meander around the atrium forming a moving barrier against any successful wave of contraction. Instead, additional wavelets are created from these unsuccessful attempts. Hence, there is no P wave, unlike in atrial flutter. Autonomic tone (especially vagal but also sympathetic) can shorten AERP and increase atrial dispersion. Hypokalemia and hypomagnesemia can also increase atrial dispersion. Atrial dispersion is also a function of atrial electrical remodeling (increased intracellular Ca). There is also structural remodeling (increase in atrial size) as well as ultrastructural or contractile remodeling. When the conduction velocity increases, the wavelets begin to disappear or fuse because the advancing waveletfront of depolarization catches up to its trailing tail of refractory tissue. The wavelets are forced to enlarge or coalesce, but then they are more likely to bump into others, canceling themselves. At some point their numbers dip below critical mass and AF is terminated. Increasing sympathetic tone causes an increase in conduction velocity (dromotropism). This latter is instrumental in terminating VMAF episodes.

Regarding the irregular rhythm of AF, I suspect that it is due to occasional wavelets of Moe that are meandering near the AV node. When their circular path intersects with the AV node, this results in a ventricular contraction. This event is random and hence irregular. At first I thought that this couldn’t happen, because my irregular rate during AF was slower during the night than during the day. This diurnal rhythm is controlled by the vagus nerve through the SA node. I couldn’t see how impulses from the SA node could flow through the barrier formed by the wavelets and reach the AV node. However, the vagus also controls the AV node by slowing its conduction velocity at night. Hence, at night fewer wavelets would result in a ventricular contraction. This then explains to me why my HR in AF is lower at night, even though no SA node originating signals reach the AV node. Thank you James D.

Dr. Van Wagoner, previously cited by Erling, is on the cutting edge of AF research and intimately involved in trying to answer questions such as those posed by Dieter. Two teaser articles by him are:
Molecular Basis Of Atrial Fibrillation: A Dream Or A Reality?
J Cardiovasc Electrophysiol. 2003 Jun;14(6):667-9
and
Electrophysiological Remodeling In Human Atrial Fibrillation.
Pacing Clin Electrophysiol. 2003 Jul;26(7 Pt 2):1572-5
by Van Wagoner DR.
Department of Cardiovascular Medicine, Cleveland Clinic Foundation, Cleveland, Ohio 44195, USA. vanwagd@ccf.org

So, Dieter, I have to agree with you in that LAF is primarily a cardiac problem and not an autonomic one.

PC v54

P.S. Many of the references for the above may be found in the Proceedings of the Conference Room, Session 14A

PC,

In your last sentence, you made the statement that you didn't believe AF was an autonomic problem. This situation was posed to me, while away on my trip, and my first thoughts were autonomic dysfunction. The woman cannot control her bladder, and is having a second operation to remedy the problem, but she is also having problems with GERD. It sounds as if both sphincters are being overstimulated by the PNS. Perhaps free glutamate?? What are your thoughts?

Richard

Richard,

In a recent post on the BB you included a web link to an article by Dr. Clapham at Harvard on potassium ion channels.

http://clapham.tch.harvard.edu/researchtopic.html?subject=girks

In the bibliography at the end of the article there was a reference to

Evaluation Of The Role Of IKACh In Atrial Fibrillation Using A Mouse Knockout Model, Kovoor, K, Wickman, K, Maguire, CT, Pu, W, Gehrmann, J, Berul, CI, and Clapham DE., Journal of the American College of Cardiology. 2001, 37(8), 2136-2143.

I was able to locate this article in the medical library in our hospital. In it his research team details how they were able to show that this specific K channel is essential for VMAF (in mice) and AF could not be initiated in its absence.

As I indicated in my BB post on 11/3/03, many of the newest pharmaceuticals presently in the pipeline operate via these ion channels that act in an aberrant manner during AF – tarantula venom and RSD 1235, etc.

As detailed in a post on the BB on 7/12/03 by Carol and Kerry about recent findings on the genetic mutation of AF out of China Dr. Xu, leader of the research team said, "Most people with the condition will not have any mutation," he says. "They are most likely to have some kind of polymorphism," a subtly different gene."

A polymorphism is defined as an alternate form of a gene present in greater than 1% of the population.

So I think that the ion channels, especially the K channels, are the final common pathway for AF. So it would appear that the "defective substrate" of at least VMAF is an ion channelopathy. And like most diseases there is a genetic component and an environmental component. The latter is probably due to oxidative damage to the cell wall where the channels are located and the former constitutes the predisposition. I wasn't born with AF, but like many others, led a lifestyle that potentiated this predisposition. A magnesium shortfall, too much aldosterone (dehydration, stress), insufficient daily dietary K and antioxidants, etc., combined over time to unmask this.

Also, I neglected to answer Dieter question about what might be happening with the SA node during AF. As previously posted on the BB on 11/3/03 "baroreceptor mediated reflex bradycardic responses are markedly enhanced by ANP". This suggests that the ANP secreted by the atria during AF and tachycardia might be causing the SA node to decrease its rate of firing, making conversion to NSR even less likely.

PC v54

PC:

Please rephrase "The frequency of PAC PAIRS is inversely proportional to the time interval of the next episode of AF" in simpler terms. It sounds to me like you are saying the more PACS PAIRS you have the longer it will be until AF begins, but I have the feeling that's not what it really means.

Dr. Natale & Nurse Michelle at Cleveland Clinic and just about every other health care person who I'ved asked over the years have pooh poohed my concerns about PACS.

I'm learning from the BB & Hans and now you(?) that there may be a reason to be concerned about PAC'S.

Thanking you in advance,

p.s. when posters mention dietary K are they referring to vitamin K or potassium?

njb

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njb,

Below are three abstracts that underscore this inverse relationship, i.e., the HIGHER the frequency of PACs (especially pairs) the LOWER the time interval until the next AF episode. It also appears that it's not just the frequency of PACs per se that determines ones risk of an episode but the time interval between PAC pairs. The LOWER this time interval between pairs the LOWER the time interval before the next AF episode.

AF Episodes Preceded by Premature Beats
German researchers have confirmed that most atrial fibrillation episodes are preceded by a series of atrial premature complexes (APCs). They analyzed 297 paroxysmal AF episodes in 33 patients and found that the APCs (ectopic beats) originated in the left atrium in 77.5% of the episodes. The frequency of APCs increased from an average of 0.8 APCs per minute to 4.1 per minute in the two minutes preceding the beginning of an episode.
American Journal of Cardiology, Vol. 88, October 15, 2001, pp. 853-57

Paroxysmal Atrial Fibrillation: Ectopic Atrial Activity and Prevalence of Severely Symptomatic Patients.
Pacing Clin Electrophysiol. 2003 Aug;26(8):1668-1674, Jensenc et al.,
Department of Cardiology, Gentofte University Hospital, Copenhagen, Denmark.
Catheter ablation is a promising approach in severely symptomatic patients with paroxysmal atrial fibrillation (PAF). Until this time it has only been performed in highly selected patients with weekly episodes and frequent premature atrial contractions (PACs). The aim of the present study was to estimate the prevalence of severely symptomatic patients with PAF and to evaluate the significance of PACs. The files of 7,447 consecutive patients were screened and 1,357 PAF patients identified. Holter recordings were performed in 108 patients with >/=2 spontaneous AF episodes. Despite antiarrhythmic treatment, 6.5% (1.8-11.1%) had a history of weekly PAF episodes. 29.2% of patients and 10% of healthy, age-matched controls had more than 700 PACs. The number of PACs was inversely related to the reported numbers of previous episodes and directly related to age and size of left atrium. We estimate that about 6.5% of patients with PAF are severely symptomatic and might benefit from catheter ablation. Our data suggest that the number of PACs should not be used as a selection criterion for catheter ablation. Frequent PACs are seen in a substantial proportion of elderly healthy individuals. (PACE; 26:1668-1674)

A Methodology For Predicting Paroxysmal Atrial Fibrillation Based On ECG Arrhythmia Feature Analysis
W. Zong, R.G. Mark
Harvard-MIT
Cambridge, MA, USA
This work addresses the 2001 CinC Challenge for predicting the onset of paroxysmal atrial fibrillation/flutter (PAF) from the surface electrocardiogram (ECG).
"...These encouraging results indicate that APCs are indeed of great value for predicting imminent PAF ..."

PC

P.S. I don't know about others, but I never refer to Vitamin K as just K. It's always potassium.

PC states in his excellent explanatory post above:

"In addition to reentry, there must be automaticity, whereby a single atrial focus fires repeatedly (PACs)."

Is eliminating this automaticity how PVA seeks to succeed in eliminating AF - in a nutshell as it were?

Virtually ALL healthy adults get PACs - indeed, one of PC's references in another later post above cited that 10% of age-matched controls had 700 PACs each on a 24hr Holter. But these folks DON'T get AF.... so PC's surmisal that a K ion channelopathy is to blame certainly makes sense. So, what to do?? Does anyone know if human trials with

tarantula venom/peptide and RSD 1235 have yet been undertaken and the results of the same/progress otherwise to date??

Mike F.

Mike,

I don't think that PVI and ablation eliminates automaticity so much as it eliminates the ability of these "rogue cells" to impose their will on the rest of the heart. Their connection is disrupted.

Indeed I think that the presence of PACs is a function of ion channel malfunction (? oxidative damage to the cell wall as we age) and their frequency is a measure of both the number of cells involved and the extent of the damage to any of these rogue cells. Genetic factors would only magnify this.

Regarding RSD 1235, please visit
http://www.cardiome.com/investor/press/news.php?ID=105

PC

PC,

Thanks for the additional info. Let's hope that the new drug RSD 1235 will - assuming it proves safe and successful - also at some point become available orally as well as intravenously.

BTW, upon re-reading my last post, it looked a little undiplomatic in its timber. I would reiterate my great respect for your good self and your views, I did not mean in any way to imply negativity on your behalf as regards the future prognosis for Erling, and I really do hope and pray for Erling and Fran that their AF has GONE FOR GOOD!

Mike F.

Mike,

Thanks for your insightful questions, and for your kind concern. I think that your question to PC re: Fran and me is right on: "Does their experience prove that such things as fibrosis and ion channelopathies can be effectively put right??"

I greatly value Dr. Andrew Weil's book "Spontaneous Healing" (1995), wherein (for instance) he describes the continuous renewal of cell membranes: "It appears that at many points on the cell surface, membrane is forever being sucked into the cell, examined, sorted, and recycled back to the surface. One phase of this process is the recognition and elimination of defective membrane structures via lysosomes." By "membrane structures" is Dr. Weil referring to the pumps, channels, receptors, embedded in the membranes? Is self-healing perhaps a continues process in all tissues?

PC, to what extent are membrane pumps, channels, receptors, renewable? And, is fibrosis reversible?

Richard, I recall you mentioning the disappearance of a scar - fibrotic tissue - was that due to supplementing with a specific amino acid - glycine? Magnesium glycinate has been my preferred form for some time.

The stability of my heart rhythm gets better and better with time - nearly perfect now. When AF first went away there remained innumerable "rogue" beats - hundreds per day -- although they no longer initiated a-fib/flutter. Now, almost two years later, there is an almost complete disappearance of such ectopics.

I have continued on the same diet/nutrient supplements regimen that apparently got me out of AF-- the idea had been to try to optimize cell membrane integrity, optimize the cell's energy production (mitochondrial ATP production), and optimize required enzymes and their efficacy - membrane ion pumps are enzymes:

- strict elimination of trans fats
- reduction of vegetable fats (omega 6s)
- addition of omega 3s
- addition of Coenzyme Q10
- addition of high dose magnesium
- reduction of calcium intake
- addition of all B-vitamins
- increased protein intake for amino acids - protein "building blocks"

Erling, ex (?) 75 (fact)

Erling,

Are you really sure of your last fact? You don't seem to suffer from the myriad afflictions, e.g., memory loss, short attention span, etc., that assault us younger folk, much less a 75 year old.

Regarding reversal of damage, who can truly say. I suspect that at least some can be reversed. What can't be reversed at present is the genetic predisposition. Are our ion channels problematic because our genes dictate that too many or too few be produced? or that they are less efficient? or ...

What's clear is that for the foreseeable future a nutritional/dietary approach is required, if one is to avoid meds and/or the healing ray in denying admittance to the unwelcome visitor.

PC v54 (I think)

PC,

You ponder, "Are our ion channels problematic because our genes dictate that too many or too few be produced? or that they are less efficient? or ..."

What about "gene expression" being problematic? Where the genetic code is correct, but the protein formed from the code isn't? According to Craig Cooney, PhD, in his book Methyl Magic (seductive title by publisher?), "methylation" is all important in gene expression (back to nutrition): " When gene expression goes awry the results can be horrifying: birth defects, cancer, and maybe even autoimmune diseases such as lupus. When other aspects of methyl metabolism go awry the downside can be equally terrible: heart disease, mental retardation, and diseases of the nervous system, among others." Makes sense to me, but I suppose that many, many other factors beside methylation play into gene expression.

So, if proteins such as ion channels, etc., are replaceable (are they?), and if "good" ones are put in place of "bad" ones, due to corrected gene expression, and if the bad ones were the cause of the AF....

i.e. could AF sometimes be "cured" by correcting problematic gene expression?

Erling ex (I hope) 75 (just a minute ... let me check ...)

Erling,

The mechanics of gene expression (along with so many other things) is way over my head.

PC

One other thing,

Given the contents of the posts to this thread thus far, how is it that Erling and Fran have eliminated their AF?? Does their experience prove that such things as fibrosis and ion channelopathies can be effectively put right?? Or are these two individuals (whom I greatly respect and admire) merely in some form of remission?? (I sincerely hope NOT (-:). I note in one of PC's psots to a thread sometime ago that in replying to Erling he concluded his post with words to the effect of " cured though you MAY be". (Not "cured though you ARE".) No disrespect PC, but I sense reservations.....

Mike F.

Mike,

I love such direct questions. No offense perceived. Your exceedingly diplomatic approach to this CR and the BB stands in stark contrast to my own confrontational contrariness.

I think Fran would be the first to admit that her disposition to AF will forever lurk in the background waiting to rear its ugly at the first chance that her guard is lowered. Her somewhat recent very brief episode during an occasion of GREAT stress speaks to this. No one should underestimate the extreme discipline required in order to "cure" this disease. I don't think either Erling or Fran have significantly reversed the ion channelopathy. They have however, modified the risk factors and triggers that potentiate this existing predisposition.

PC

I have to agree PC I would be the first to agree that AF will always lurk in the background for me. But I do know exactly what causes it in me so avoidance is now easy and is second nature. Vigilance in the beginning is key but I don't need to think about it now - only stress and total hunger leads to me taking a risk - and I will try my utmost never to be in a situation like that again.

I have to agree with Erling's post about gene expression. I have read that many things such as MSG can change gene expression and it can even be passed onto offspring. I am hoping that my gene expression will clear up but due to family history I think my expression has been passed on. Unfortunately I ate it through each pregnancy so am fairly sure all my children are affected and history is now repeating itself with me telling my kids not to eat it and them reacting just like me..... but at least they will be forearmed when it comes to trying cures for anything that ails them in the future.

Fran

PC,

The Cleveland Clinic article 'Innovations: Research in Atrial Fibrillation' by David Van Wagoner, PhD that I cited in a recent post contains the following statements, and two very descriptive micro-photographs of normal cardiac tissue vs. cardiac tissue with fibrosis. The idea that fibrosis (resulting from inflammation?) underlies (some?) AF prompted me to ask if fibrosis is ever considered to be reversible:

http://www.clevelandclinic.org/heartcenter/pub/atrial_fibrillation/AFresearch.htm

Mechanisms of AF
In many patients, AF begins with short episodes, typically characterized as "palpitations" (a fluttering sensation in the chest), or "paroxysms." Over time, there is a tendency for these episodes to become longer. Why does this happen? Once AF has been initiated, the atria undergo a process known as "remodeling." AF-induced atrial remodeling causes both structural and electrical changes:

Structural changes: As shown in the pictures below, individual muscle cells within the fibrillating atria tend to become elongated and sometimes wider. In addition the space between individual myocytes typically becomes more fibrotic, with fatty infiltration, and the atria is less able to contract. These changes make it more likely that blood will remain longer in the atrial appendage, increasing the possibility of clot formation that can cause strokes.

Electrical changes: Fibrillating atria tend to have more complicated patterns of electrical activity. This is due both to the increased fibrosis, and to intrinsic changes in the electrical activity in the atrial myocytes. Research at the Cleveland Clinic Foundation has helped to characterize the electrical remodeling process associated with long-standing AF.

I asked google.com about: cardiac fibrosis reversible, which produced about 9,900 results. Here's one, an abstract of an article from the National Academy of Sciences:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11997477&dopt=Abstract

Proc Natl Acad Sci U S A. 2002 May 14;99(10):7160-5. Epub 2002 May 07.

Reversible cardiac fibrosis and heart failure induced by conditional expression of an antisense mRNA of the mineralocorticoid receptor in cardiomyocytes.

Beggah AT, Escoubet B, Puttini S, Cailmail S, Delage V, Ouvrard-Pascaud A, Bocchi B, Peuchmaur M, Delcayre C, Farman N, Jaisser F.

Institut National de la Sante et de la Recherche Medicale U478, Hopital Bichat-Claude Bernard, AP-HP, Federative Institute of Research 02, 75870 Paris, France.

Cardiac failure is a common feature in the evolution of cardiac disease. Among the determinants of cardiac failure, the renin-angiotensin-aldosterone system has a central role, and antagonism of the mineralocorticoid receptor (MR) has been proposed as a therapeutic strategy. In this study, we questioned the role of the MR, not of aldosterone, on heart function, using an inducible and cardiac-specific transgenic mouse model. We have generated a conditional knock-down model by expressing solely in the heart an antisense mRNA directed against the murine MR, a transcription factor with unknown targets in cardiomyocytes. Within 2-3 mo, mice developed severe heart failure and cardiac fibrosis in the absence of hypertension or chronic hyperaldosteronism. Moreover, cardiac failure and fibrosis were fully reversible when MR antisense mRNA expression was subsequently suppressed.

Erling ex75 (I looked it up)

PC,

Recently (11-05-03) you posted, under "Remodeling", an excerpt from an article entitled Drug Therapy for the Management of Atrial Fibrillation: An Update" at http://www.medscape.com/viewarticle/462549

That article states, "It is theorised that blockade of angiotensin II prevents atrial electrical remodelling by decreasing atrial stretch, modulating refractoriness, interfering with ion currents, modifying sympathetic tone and stabilising electrolyte concentrations".

(Your post is at http://www.yourhealthbase.com/forum/read.php?f=3&i=1559&t=1559)

An article dealing with ACE inhibitors in regression of cardiac fibrosis, Cardiac Fibrosis as a Cause of Diastolic Dysfunction, is at http://www.bnk.de/herz/en/1922_3110.htm

Although this article is not about AF, it reports "regression of established cardiac fibrosis by its presumptive proteolytic digestion induced by ACE inhibition....".

Erling

Erling,

Interesting and encouraging phrases:

"antagonism of the mineralocorticoid receptor (MR) has been proposed as a therapeutic strategy." (for reversal of fibrosis)

"It is theorised that blockade of angiotensin II prevents atrial electrical remodelling by decreasing atrial stretch, modulating refractoriness, interfering with ion currents, modifying sympathetic tone and stabilising electrolyte concentrations"

"regression of established cardiac fibrosis by its presumptive proteolytic digestion induced by ACE inhibition....".

From your above posts.

So, how - through diet - can we antagonise the MR, block angiotensin II, and inhibit ACE??!!

OK, OK, I'm being stupidly flippant and over-simplifying, but your diligent searching certainly appears to indicate that fibrosis is indeed reversible - possibly by a number of mechanisms (but I guess this might depend on what causes the fibrosis in the first place?). There ostensibly would appear no solid reason why modified diet could not bring about some of the necessary processes to reverse cardiac damage. (Short pause whilst I finish my bowl of rabbit (wild) and broccoli (organic).)

I'm looking forward to PC's take on your articles given that he is obviously a bright chap and is used to the terminology involved (which, I'm happy to admit, leaves me more than a little braincramped - though I do grasp the gist in simple terms).

Good to have you back on board Erling - and particularly good to have you as such as living proof that AF CAN be kicked in the butt.

Mike F.

Hello Erling and All,

I've been pretty drugged out from my trip, but I would like to add some thoughts and what I have observed about myself. While I was away, my diet went completely out the window. We were with a group of friends, so I went with the flow. I tried to eat a decent breakfast, but the rest was pretty bad, yet I didn't go out of rhythm. I thought at one point I would, but didn't. We were eating out in taverns and at the football game, so you know what kind of food that is. I'm sure I had a dose of MSG somewhere, with a few nitrates thrown in. Is it the supplements and aminos that I'm taking, along with molybdenum everyday? I even had a couple of drinks.

Second thing I found very interesting about the chicken pox herpes on my left butt cheek is that it moved. While taking higher doses of lysine, but I must mention also taking alpha lipoic acid, proline, taurine and carnitine, in case the combo might be relevant, is when my scar almost completely disappeared. I attributed it to lysine, because it is a well known fact that this amino helps this scenario. I have had this for years, in the same exact location, and have no idea how I contracted it. In any case, I thought that I might have ridded myself of the herpes because of the almost complete disappearance of the scar, but it showed up once again, and had moved to a different location. On the same cheek but several inches below the original spot. So my thoughts are that the tissue healed, but the body did not rid itself of this virus.

The two above scenarios tell me one thing; that these supplements and aminos are doing something within my body. If

I remember correctly, Carol was also taking lysine, as well. My regimen by Dr. Gersten does not include lysine, except in a blend, but I think if we all focus on the aminos that restore tissue, we might be surprised. I do believe that the addition of sulfur by way of methioninie, N-acetyl-cysteine, alpha lipoic acid and/or reduced glutathione could also have miraculous results, as this forms disulfide bonds. In my opinion, I believe that the combination of alpha lipoic acid, proline and lysine were the key ingredients of my tissue healing.

I don't know what to add about the K channel that PC refers to, but what I do find interesting is that so many people around me have the same problem. I know more people with arrhythmias than with anything else combined. Why is that? I still maintain that we are all seriously deficient in sulfur, and without enough sulfur, we start to have tissue breakdown and toxic element buildup. I know I've gone off on tangents of phosphorous, molybdenum, serotonin, etc., and that all the elements are of equal importance, but the sulfur has so many far reaching effects within the body and seems to be the one deficiency that we could all share. We all eat differently, some eat more meat, and some more vegetables, some eat out, some don't, but we all breathe the same polluted air, sit behind the vehicle's exhaust, eat the meat from the animal that is deficient in sulfur due to fighting its own problems, eat the fish with mercury, etc. Remember the study about fish and mercury. The mercury in the fish would combine with the cysteine to form methylmercurycysteine, and this would pass through the human body. So was any cysteine left in the fish for human absorption?

Richard

I found some interesting information of bismuth and magnetism, and posted on the BB, but thought I'd put the link here for future reference.

http://www.yourhealthbase.com/forum/read.php?f=3&i=1913&t=1913

Richard

Some food for thought about magnetism:

Another relationship between electricity and magnetism is that a regularly changing electric current in a conductor will create a changing magnetic field in the space about the conductor, which in turn gives rise to a changing electrical field. In this way regularly oscillating electric and magnetic fields can generate each other. These fields can be visualized as a single wave that is propagating through space. The formal theory underlying this electromagnetic radiation was developed by James Clerk Maxwell in the middle of the 19th cent. Maxwell showed that the speed of propagation of electromagnetic radiation is identical with that of light , thus revealing that light is intimately connected with electricity and magnetism.

Well, I lost the address, as I hit control V instead of C in the field. This could be a stretch to some extent, but strangely, looking at the field of magnets is almost like looking at the circular motion of AF.

Richard

I have been doing some more research. Surprise, surprise. In light of what Erling has posted about reversing fibrosis, it made me do a search on Valerie Hudson's research on Cystic Fibrosis and Glutathione. She was driven to research, in order to cure her children. In the following link under Fundamental Papers-Rethinking Cystic Fibrosis, there were several interesting points made. The lungs have 140x's more GSH than the normal levels of extracellular GSH in blood plasma. pg. 2 I found this of interest, because the blood leaves the lungs and then feeds into the pulmonary vein to the left atrial. If the lungs are lacking in GSH, could this cause damage to the pulmonary vein and the surrounding tissue of the left atrial? NO and GSH appear to regulate all energy metabolitism. pg 6. Loss of GSH causes inability to maintain appropriate levels of phosphatidylcholine. pg. 4. GSH depletion reduces smooth muscle relaxation in response to NO. I think you will all find this study very important.

http://members.tripod.com/uvicf/research/glutathione.htm

I then was reading about idiopathic pulmonary fibrosis. Here's a link that I found quite interesting.

http://www.gethealthyagain.com/idiopathic-pulmonary-fibrosis.html

Pay particular attention to glutathione and also the candida self test, using saliva. I did the test, and had many strings hanging in the the solution of water, indicating high candida. I knew I had high levels from my testings, and this confirmed it.

If you go to this link, on the same site, you can read about ThreeLac which has had good results in ridding oneself of Candida:
http://www.gethealthyagain.com/supplementreport.html

Any thoughts would be appreciated.
Richard

Whether LAF is reversible or not seems to be a popular question. I plead ignorance on differentiating gene from gene expression, at least at the molecular level. I personally think that invoking such a thing is a needless complication. So let me try to build a case for genetic LAF and leave the gene/gene expression matter to others.

LAFers have a problem adapting physiologically to any given HR (loss of the physiologic rate adaptation). Rate adaptation is a function of atrial effective refractory period (AERP). LAFers have a shorter AERP (v. those with NSR and no history of AF) at any given HR. In fact AERP during AF is a predictor of cardiovertibility. The shorter the AERP the more difficult the cardioversion. The real question seems to be whether this shortening is the cause of AF or caused by it.

"Electrophysiological Changes in AF"
http://www.ub.rug.nl/eldoc/dis/medicine/a.e.tuinenburg/appendix_1.pdf

Let's put this latter question aside for a minute and look more closely at AERP, because I think this will provide some insight into the answer. AERP is shortened by the vagus nerve through opening of the muscarinic gated (M2) IKACh potassium channels that we've been discussing. The action of this ion channel is determined genetically.

"Evaluation of the Role of IKACh in AF Using a Mouse Knockout Model", Clapham et al., JACC, 37 (8):2135-2143 (June 15, 2001).

This is further aggravated by any inhomogeneity of vagal nerve fibers in the heart and its associated dispersion of refractoriness. This is admittedly a mouthful, but parhaps the following analogy will make this more clear. Think of the mass in the universe as analogous to the nerve endings in 3D atrial tissue. We all know that mass in the universe is not uniformly distributed (it is not homogeneous) but has a certain "clumpiness". Indeed we live on one such clump. This lack of uniformity in the distribution of vagal nerve fibers in the atria (which are responsible for AERP) translates to a certain variation in AERP from one atrial cell to the next. This feature is called dispersion of refractoriness. No one has a completely smooth distribution. I'm sure that if you were able to measure this dispersion (at any given HR) in any population, you would get a bell shaped curve. Those with LAF must come from the ranks of those with more "clumpiness" to these nerve fibers with its associated greater dispersion.

"Pathophysiological Mechanisms of AF"
http://www.ub.rug.nl/eldoc/dis/medicine/r.g.tieleman/c2.pdf

The above website contains an excellent explanation of the electrophysiology of AF. The following is an interesting passage that will be of interest to those considering ablation:

"This demonstrated that in the right circumstances (vagal stimulation shortens the refractory period, which shortens the wavelength, see below) AF did not depend on the rapid firing focus any more, which
convinced people that AF was a reentry arrhythmia.. However, recently, Jais and colleagues demonstrated a focal

mechanism in patients with AF similar to the experiments by Scherf. In these patients a fast firing focus, typically originating from one of the orifices of the pulmonary veins, causes fibrillatory conduction to the surrounding atrial tissue with identical electrocardiographic characteristics as the more classical forms of multiple wavelet AF. However, patients with this so-called focal AF can be cured by ablating the single fast firing focus, whereas patients with AF based upon multiple wavelet reentry do not benefit from ablation of a single site. Therefore, in focal AF, the induction and perpetuation of AF is different from the mechanisms explaining the initiation and perpetuation of multiple wavelet AF, which are described below. The percentage of patients with AF that could be cured by this focal approach is not known."

In the article Genetic Mutation Linked to Atrial Fibrillation , which appeared January 09, 2003 Xu, leader of the Chinese research team, said, "Most people with AF will not have any mutation. They are most likely to have some kind of polymorphism, a subtly different gene." A polymorphism is an alternate form of a gene present in more than 1% of the population.

So there you have it. On the one hand we have an expert, who knows far more about such matters than I, stating that LAF is probably due to some polymorphism. On the other hand we have a gene (not present in these knockout mice in whom AF uniformly could not be initiated) that is "essential for the profibrillatory effect of vagal stimulation". This same gene (potassium channel IKACh) is responsible for AERP, which in turn is the cause of "the loss of physiologic rate adaptation", the very problem that plagues all LAFers.

There is even more evidence that a polymorphism of IKACh is the culprit. So far we have not mentioned PACs. They are required in order to trigger AF, at least vagally mediated AF (VMAF). "IKACh is very important in maintaining and hyperpolarizing the resting membrane potential in atrial cells." If this membrane potential is not maintained, the cell will discharge (PAC).

So here we have one gene controlling all that goes awry in VMAFers, AERP, dispersion, PACs.

Now let's turn our attention to adrenergic LAF. Sympathetic activation further shortens the AERP, but less than does vagal stimulation. However, catecholamines are potent triggers of PACs due to the associated increase in automaticity. So if there were some other reason for dispersion of this AERP, e.g., fibrosis, AF could easily result. Under stress not only are mineralicorticoids (like aldosterone and cortisol) from the adrenal cortex increased but also catecholamines from the adrenal medulla. The former are responsible for cardiac fibrosis (dispersion) and the latter provide shortening of the AERP and increased PACs. All the necessary ingredients for LAF are present. However, not everyone under stress is susceptible to LAF. Adrenergic LAFers also have "loss of the physiologic rate adaptation". Perhaps they also have a polymorphism of IKACh.

Now let's take a look at hypoglycemia. There is an excellent article entitled "Channelopathies Of Inwardly Rectifying Potassium Channels" at http://www.fasebj.org/cgi/content/abstract/13/14/1901

"Kir channels are ubiquitously expressed and serve functions as diverse as regulation of resting membrane potential, maintenance of K+ homeostasis, control of heart rate, and hormone secretion. In humans, persistent hyperinsulinemic hypoglycemia of infancy, a disorder affecting the function of pancreatic ß cells, and Bartter's syndrome, characterized by hypokalemic alkalosis, hypercalciuria, increased serum aldosterone, and plasma renin activity, are the two major diseases linked so far to mutations in a Kir channel or associated protein."

So there may be a simple reason why hypoglycemia is increased in LAFers (26% according to Hans' most recent survey). This Kir polymorphism may be of IKACh, one of the Kir channels.

I've cited before the following references

"The refractory period was shortest under hypoglycemia in the left atrium and longest under normo or hyperglycemia in the right atrium."
"Susceptibility Of The Right And Left Canine Atria To Fibrillation In Hyperglycemia And Hypoglycemia".
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8501411&dopt=Abstract

"Our data indicate that hypoglycemia causes an acquired long QT syndrome. Sympathoadrenal stimulation is the main

cause, through mechanisms that involve but are not limited to catecholamine-mediated hypokalemia."
"Mechanisms of Abnormal Cardiac Repolarization During Insulin-Induced Hypoglycemia"
http://diabetes.diabetesjournals.org/cgi/content/abstract/52/6/1469

Long QT syndrome is caused by a potassium channelopathy. Could the hypoglycemia induced acquired long QT Syndrome involve a similar mechanism? Persistent hyperinsulinemic hypoglycemia of infancy involves a Kir channelopathy. Are LAF and its oft associated hypoglycemia due to a IKACh channelopathy?

Have Fran and Erling cured themselves? Well the simple answer is yes and no. They've probably repaired the damage done via oxidizing agents to their cell membranes (where ion channels are located) and have sufficiently restricted further exposure to such agents. They may have even reversed any fibrosis. However, I believe their genetic predisposition remains. And I believe this genetic predisposition is an IKACh polymorphism.

Since Dieter hasn't checked in, I suspect that he (and no doubt many others) must think this to be no more than just a bunch of fancy mumbo jumbo.

PC, MD (mumbo dumbo) v54

PC

Well you have done it again. I have to say that your argument about AF being caused by a fault in the IKACh channel seems to fit with my experience of AF, hypoglycemia and once my GP said that my ECG showed 'slightly elongated QT wave" This topped with my seizures, near death experiences and heart going awry prior - after being woken with an alarm or phone etc fits the symptoms for long QT. But my cardio said the two were not related.

Unfortunately, I have to agree (in my case) that I feel from experience the underlying fault will always be there. I know I am a high oxidiser and summarize that I have slowed oxidation rate through diet and loads of natural antioxidants.

I wonder how Erling feels about this theory....?

Can you explain the difference between polymorphism and genetic mutation? On the surface of it they sound like very similar problems, but then I can be a bit simplistic.

All the best,
Fran

PC,

I can't for sure agree or disagree with you, but you sure give a good argument. I have to say that I hope you're wrong. That paints a bleak picture. I have one question however. Just off the cuff, what is your opinion of polymorphisms in ALS, Parkinson's, and Alzheimer's? Also, I wonder if there is a test for this polymorphism?

Richard

Richard,

The next sentence in the article abstract that I cited about diseases presently associated with Kir channelopathies was "In addition, the weaver phenotype, a neurological disorder in mice, has also been associated with mutations in a Kir channel subtype. Further genetic linkage analysis and full understanding of the consequence that a defect in a Kir channel would have on disease pathogenesis are among the priorities in this emerging field of molecular medicine."

The weaver phenotype is a neurodegenerative disease of the cerebellum.

There is another disease in fruit flies called shaker mutant that is caused by a Kir channelopathy.
Episodic ataxia in humans is very similar to shaker disease in fruit flies and is also due to a similar channelopathy.
Please see
http://pub.ucsf.edu/missionbay/science/jan.php
and
http://www.hhmi.org/research/investigators/janly.html

So neurodegenerative diseases would have to be at the top of the list for diseases associated with a Kir channelopathy. Kir are critical in both muscle and nerve tissue because of their signal propagation.

Molecular physiology is tremendously complex. Testing for such polymorphisms is not exactly around the corner. I'm more interested in any drugs that might specifically address our potassium channelopathy. I don't need to know if or how or why just that it'll work.

Presently work is proceeding in this area on tarantula venom, scorpion toxin and Conus purpurascens toxin from cone shells. Maybe RSD 1235 will come to our rescue before ablation techniques are sufficiently perfected.

PC

PC,

Just to say thanks for a really interesting couple of posts (and thanks of course to James and others also for their input). An earlier sentence of your longer post struck a chord in particular:

"LAFers have a problem adapting physiologically to any given HR (loss of the physiologic rate adaptation)."

This goes hand-in-hand with my own observations of myself that I seem to experience PACs (and occasional AF) just at those times when there is a change in my HR..... PACs usually occurring when a sudden change in HR occurs - such as when tripping up on foreshore rocks! I see the sense in thinking of this in such a way whereby my AERP isn't keeping up with my HR as it changes.

Given that "AERP is shortened by the vagus nerve through opening of the muscarinic gated (M2) IKACh potassium channels", would a selective potassium channel blocker such as Tikosyn be accordingly particularly useful if blockade is required?

Of possible peripheral interest form a 2003 Hungarian abstract at:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12866149&dopt=Abstract

"The authors summarize the up-to-date knowledge relating to the pharmacological treatment of atrial fibrillation. They emphasize that drug treatment continues to be in the forefront of the therapy of the arrhythmia, which can now be considered to constitute a cardiovascular epidemic."!!!

And:

"The clinical introduction of procedures based on myocardial gene therapy is now a realistic therapeutic approach as concerns atrial fibrillation too." ??????

How are you getting on with the Norpace these days? Is it still successfully converting your fortnightly/three-weekly (?) episodes within an hour or two?

Mike F.

No, PC, not mumbo-jumbo at all. I just need time to digest all the postings so far.... Every little bit (and in your case a rather large bit...) helps me to understand better what I am faced with. I still feel that more attention ought to be devoted to exploring shortcomings in the SA node / conduction system. If these could be strengthened in some way, we might, I think, make some progress towards alleviating matters for Afibbers. Thanks - and sorry about being a bit tardy with my response.

Best regards,
Dieter

This an interesting thread! I can't really add much to PC's excellent comments, I think he has hit the nail on the head. However it's 5:00am and I'm currently going at 140 bpm and can't sleep so I thought I'd have a go a contributing something - I hope some of it is useful :)

In no particular order....

<Dieter >"... These spinning wavelets generate discharges at a rate of 300 ? 350 / minute, possibly even faster..."
Some of these rotors/wavelets go at a very high frequency, with an action potential duration (APD) of less than 60 ms some of them can run at 16-18 Hz (just over 1000 per minute!). Some of the rotors are long lasting (minutes/hours) Some of the wavelets are extremely short lasting (100ms and less) - it's very dynamic!

<Dieter >"...Since the contractile tissue in the atria will always follow the fastest frequency, the SA node with its inherent beat of 60 ? 80 / minute stands no chance."
Whilst I've found this to be true once I've been in AF for any length of time, if I'm quick enough as soon as AF kicks in if I jump out of bed an move around I can quite often knock myself back into NSR for a short period of time. I believe its because I'm reducing the amount of Acetylcholine (ACh) which, whilst I agree with the ion channelopathy theory, I still believe ACh plays a big part. See later for more on this.

<Dieter >"...What sets off the activity of these wavelets"
Fundamentally it's bad timing/conduction. If you combine low APDs with poor dispersion you are asking for trouble. Ectopics are an ideal thing to kick the system into AF, but I personally don't believe they are a necessity. (I also don't believe that "In addition to reentry, there must be automaticity, whereby a single atrial focus fires repeatedly". I accept that automaticity can kick AF off and focal AF, where the automaticity continues, accounts for a lot of AF but I believe AF can also be self sustaining with no apparent source. I wonder how many of us are in the overlap group - where some rogue cells rapidly fire and kick us into AF but then stop automatically firing but the AF remains?

<Dieter >"...and what makes it stop (in paroxysmal LAF)"
Good timing :) Lengthen the ADP and the wavelets can't chase their tails.(they hit refractory cells and have nowhere to go - note that this happens all the time in AF too but there's enough wavelets that manage to re-enter to keep the system in chaos). If the dispersion is good enough when the APD lengthens you've got favourable conditions for NSR. There's obviously the fuzzy area when both AF and NSR could exist. It's my experience that this fuzzy period lasts longer before AF starts than when it ends. (When I've returned to NSR, after 24+ hours of AF, steady NSR with zero ectopics seems to be the instant state my heart is in and it's quite unlikely ectopics or AF will appear for several days)

<Dieter > "Do the active wavelets follow the rule that the fastest horse wins?"
Yes, on a local scale. Any wavelet that manages to trigger a cell will stop another neighbouring wavelet triggering that same cell (for 60 ms or longer depending on the ADP in that region).

<Dieter>"When the heart is beating normally, i.e. in NSR, each impulse travels from the SA node throughout the right atrium into the left atrium and down, through the AV node, into the ventricles. This seems to be essentially a straight-line propagation, each cell passing on the ?contract!? instruction to its next neighbour. It is, however, not clear to me how wandering islets of circular currents who are active within a circumscribed area or space can affect all contractile tissue in both atria."

I think this is because you are being a bit too strict with the wavelet description. Its a simplification of what is actually going on in an attempt to describe the chaos. It's too easy to visualise these things as nice circles (or even cylinders)

but it's a bit like describing air turbulence as circles of rotating air. Each cell passing on the contract still applies (but it can only be passed on if a. the cell that receives the message is ready to fire again and b. there's not some fibrosis in the way preventing the conduction). Although some wavelets (mother rotors) can be static most of the wavelets are extremely dynamic. (it's worth visualising meandering lines / lightning strikes for a lot of the activation rather than half a dozen neatly spinning circles)

<Dieter>"Finally this question: In AF we are dealing with an electric phenomenon. Have you in your wide-ranging searches come across any report that magnetic-field therapy has been shown to be of benefit to afibbers?"

Ah, if only we where driven by physics rather than biology :) I think it's worth bearing in mind this electricity is the movement of several different ions (rather than electrons) and much of this movement is through pumps that actively do some work (as well as passive channels). In my view this means we are not dealing with an electric phenomenon, it's more of a transportation problem.

and some other random bits...

OK, if it isn't hard enough thinking about this as a 2D problem the truth is its a 3D one. Just some of the things this introduces are...
Some natural anatomical features are ideal structures for activation to spin around - and they add to the dispersion problem, especially at the boundaries like the transiton from heart to vein up the PVs.

Rather annoyingly where the atrial wall gets thick (> .5mm) the timings of cell activation can vary with depth (and the variation increases as the frequency increases) - We've got some shear stress in these tornadoes :)

http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8319340&dopt=Abstract

paraphrasing from
"Mother rotor and fibrillatory conduction: a mechanism of atrial fibrillation"- Cardiovasc Res. 2002 May;54(2):204-16. Jalife J, Berenfeld O, Mansour M.
abstract at
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12062327&dopt=Abstract

An APD of less than 60ms cannot be explained on the basis of a relatively large IKr (whose time constant is 135 ms at +10mV).Continuous vagal stimulation, ACh perfusion or other manipulations capable of reducing APD to extreme values are necessary for AF to be established and maintained....They surmise the pro-fibrillatory effect of ACh is related to the inherent spatially heterogeneous response to muscarinic activation, which lead to an increase in AF source frequency on one hand, and spatial dispersion of local frequency on the other.

Wearing my novice hat to try to make sense of of all this :)
Lets say I'm lying in bed and I get some ectopics that throws me into AF. Is my bodies natural response to this "oh no, my heart is beating faster than it should be, I'll slow it down my throwing some ACh at it." If it is, then this is just about the worst thing it can do at the worst time - and may explain why if I'm quick enough and jump out of bed I can get back into NSR (stopping ACh runaway :)

Hope some of this makes sense - my brain is not at it's most alert at 5am after 12 hours of AF :)

All the best
--
James D

Thanks, James, for your very helpful response. It helps me towards a better understanding of what happens during an AF episode. I still have to digest some aspects of what you've said and quoted. I will probably come back to you at some later stage.

Best regards,
Dieter

Mike,

Thank you for asking about my experience with Norpace.

Disopyramide (Norpace, Rythmodan) has been tremendous for me. It has completely eliminated vagal maneuvers as a trigger for AF. I've not experienced an episode longer than 2 hours. I believe episodes are less frequent due to higher levels of the neurotransmitter glutamate required to trigger AF. Higher levels are required because disopyramide blocks the M2 receptor sites in the heart. More acteylcholine must be secreted by the vagal nerve fibers to create the necessary shortening of the AERP and associated dispersion. The shortened episode duration is due to the subsequent equilibrium reaction (rate of substance removal is directly proportional to concentration of the substance). And, of course, it also takes less time to reach the concentration of glutamate below which an episode cannot be sustained.

Although I still get occasional (some experimentally induced) episodes they all seem to boil down to one of two triggers. The most common is Chinese food. It is very predictable. Approximately five hours after eating such food AF will be triggered. It's like clockwork. I've carefully noted the time of the meal and the time of the subsequent AF episode. I've even tried taking an extra dose of disopyramide (regular release) at 9PM, which will peak around 1PM, after eating Chinese at 6:30PM. I'll still go into AF around 11 – 11:30.

I believe this happens for the following reason:
MSG from Chinese food gets into the blood and from there it has easy access to the cerebrospinal fluid (CSF). From there it takes about 4-5 hours to diffuse from the 4th ventricle (containing CSF) to the nucleus tractus solitarius (NTS) in the medulla oblongata. Formalin infiltrates tissue at the rate of 1mm/hr. This may be slightly faster in the brain because it is the softest least dense organ in the body. The location of the NTS and the dorsal motor nucleus of the Xth cranial nerve = vagus (DMNX) wrt the 4th ventricle appears to be about half a centimeter. See
http://webteach.mccs.uky.edu/COM/DLOTW_cd/na_images_fr_2b.html
for actual photos demonstrating how close the NTS and DMNX are to the fourth ventricle (images 5, 6, 7). This increases the pool of extracellular glutamate in the synaptic space around the neurons in both these locations, causing greater vagal tone and triggering an episode.
It appears that the increasing concentration of synaptic space glutamate outweighs the increasing concentration of blood disopyramide.

The second trigger appears to be hypoglycemia. These episodes occur in the late morning, when my disopyramide concentrations are lowest. I take SR tabs at 6AM, 9AM, noon, 3PM, 5PM, 6PM, 9PM. These SR tabs peak in 5-6 hours with a half life of about 10-20 hours. They occur on days when I've been remiss in eating a good breakfast, e.g., just a turnover. I believe that hypoglycemia can easily trigger VMAF (see previous CR posts). See p. 63-64 of Hans' book. LAFers typically have a flatter GTT curve in response to a high glycemic food.

I'm now on a nice AF free run. But I have to assiduously avoid Chinese food (or any other obvious source of glutamate, e.g., seaweed in sushi) and always eat a good breakfast with protein. The latter will mute the insulin response to any accompanying sugar. I also make sure to snack on low glycemic foods (nuts and berries) in anticipation of a lengthened time period between meals. Fran is the queen on this topic and these techniques.

PC

Hi, James

It seems I gave the impression that I intended to use (electro-) magnetic fields to intervene directly in an AF episode. Not at all: I am quite aware that my heart doesn't contain coils and resistors and capacitors. Sorry that I did not express myself clearly enough.

I was thinking more along means to influence cell activity. You probably know TENS units (Transcutaneous Electrical Nerve Stimulation). These are touted (and perhaps effective) for the treatment of pain. A more advanced type is the APS (Action Potential Stimulation), again primarily intended for pain relief, but some success with osteoporosis has also been reported.

The most advanced type is the BEMER 3000 developed and made by Innomed. 'BEMER' stands for this mouthful: Bio-Electro-Magnetic-Energy-Regulation. Rather unwieldy... Nevertheless: The BEMER comes in two packages, one being a mat for a full-body electro-magnetic 'massage', and a hand-held applicator for the treatment of localized areas.

The interesting thing is that specific pulsing e-m fields penetrate the whole body and work at the cellular and possibly mitochondrial level. This made me wonder whether MF-therapy could perhaps be usefully employed if my supposition has some merit that AF - at least in certain cases - might have its origin in a weakened SA node and its associated conduction system. If the cells making up this entire system have become weak - might not stimulation via appropriate electro-magnetic fields strengthen it?

I have been in touch with the research director at Innomed, but he will be able to respond to a number of questions that I put to him, only around mid-December. If anything interesting or useful transpires, I will let you know.

Regards,
Dieter

Hi, PC

Your reference to the Tieleman paper is much appreciated. It helps me towards a better understanding of the AF process. Thanks!

You may want to look at my post today to James - any comments, perhaps?

Regards,
Dieter

Thank you all for your well considered comments.

James,

I agree wholeheartedly with you EP analysis. I also don't think that a continuously firing "rogue" element is necessarily required.

As you know there are two methods used by researchers to induce AF in dogs, mice, etc. Either you give them some cholinergic or you continuously fast pace them. The former seems to be more reliable. Perhaps this gives us some further insight into the two theories, both of which have been substantiated.

The Moe theory seems to fit best with AF arising in a background of strong vagal tone. Once initiated continuous firing may not be necessary. The vagally induced shortening of the AERP and associated greater dispersion would be sufficient to fracture any incoming NSR beats, producing daughter wavelets.

The theory of Jais and Scherf "a fast firing focus, typically originating from one of the orifices of the pulmonary veins, causes fibrillatory conduction to the surrounding atrial tissue". Perhaps this theory pertains more to the adrenergic flavor of LAF. Since there is less dispersion of refractoriness, continuous firing of the rogue element is required or the episode terminates.

Also, I hope I'm clear on the direct association between vagal tone in the heart and the muscarinic gated IKACh channels. This latter is triggered by release of ACh from the immediately adjacent vagus nerve fibers. The Ach then attaches to M2 (for muscarinic) receptors and then open the IKACh channels. These are essentially only present in the

heart. There are other muscarinic receptors elsewhere in the body designated M1, M3, M4 M5. These are responsible for the dry mouth, constipation, urinary retention, blurred vision of vagolytics, such as Norpace.

Mike,

I have no doubt that the big pharmaceutical breakthrough for AF will occur when a drug is developed specific for M2 receptors. There are many Kirs (inwardly rectifying potassium channels). Other antiarrhythmics presently on the market may be K channel blockers but they are not IKACh channel blockers.

I plan to report my Norpace results and theory shortly, so bear with me. I will be most interested in hearing what you and especially Fran have to say about it.

Fran,

A polymorphism is a very old genetic mutation that has persisted and not been eliminated by natural selection. Sickle cell trait has persisted because it confers protection to red blood cells attacked by malaria. This obviously would be quite a benefit to those living in Africa or any tropical environment, at least up until recently. Hemoglobin AC and some thalassemias fill the same role wrt malaria in Southeast Asia. The real question is what benefit such a polymorphism in IKACh confers that outweighs any drawback. Perhaps it protects against diabetes.

Some of you are probably quite hesitant to buy into the IKACh/LAF connection. Some of you may be asking where does Ca and Mg fit in. After all many experts feel that increased intracellular Ca is the final common pathway for electrical remodeling. And why, more than any other supplement, is Mg so helpful?

Recent work on these two cations has revealed that there is an ion channel LTRPC7 that is crucial in this area. “LTRPC7 appears to be controlled by normal levels of the molecule ATP (adenosine triphosphate), the power source for all living cells. Recent research suggests that the LTRPC7 ion channel will become more active in situations when the body's cells run low on ATP. This can happen, for example, when the cells are deprived of oxygen or sugar, both of which are necessary for ATP production. The channel's sensitivity to the magnesium-ATP complex reveals a direct link between the LTRPC7 channel's ability to conduct calcium ions and the cell's energy level. The discovery of this relationship could have long-term implications for human conditions such as hypoxia (oxygen deficiency) and hypoglycemia (sugar deficiency).

There is another ion channel called LTRPC2. This regulatory mechanism involves a small molecule, ADP-ribose, produced by many processes in the body. Previously, ADP-ribose was considered to be a useless byproduct. However, new findings suggest that ADP-ribose is able to control the entry of sodium and calcium into cells that have LTRPC2 channels. This finding holds potential medical significance because ADP-ribose is created in large amounts by the same processes that produce free radicals and reactive oxygen species.”
Please visit
Secret Channel Holds Key to Metabolic Mysteries
http://www.bi.iup.edu/principles/lecture/classassign/LTRPC7metabolicmysteries.htm

Furthermore, no less an authority than Jean Durlach, M.D., Editor-in-Chief, Magnesium Research, President of the International Society for the Development of Research on Magnesium, and author of Magnesium in Clinical Practice feels that Mg role in maintenance of the cell membrane supersedes its critical role in production of ATP. It binds with the phospholipid layer in the cell membrane, stabilizing it and decreasing permeability.

This is where cell membrane damage wrought by ROS enters the picture. Perhaps Mg and omega 3s (thank you Jackie) reverse this damage.

Ever since Erling Waller introduced his aqueous magnesium preparation I’ve been a convert; although there was a brief period when its alkalinity bothered me (I now neutralize with a little lemon juice), I continue to benefit from the wonderful waters of Waller. In the past six weeks I’ve noticed that my leg cramps may have finally disappeared. This after a year of supplementation with just under 1000 mg/d.

PC

PC,

If I understand your theory completely, a trip to the veterinarian might be in the cards.

It is well known that the interaction between M2-muscarinic receptors and GK is blocked by the toxin from Bordetella pertussis (PTX) (Ui, 1984; Kurose et al., 1986).
http://pharmrev.aspetjournals.org/cgi/content/full/50/4/723

Richard

I guess I had forgotten about the GIRK 4 gene of the M2 receptor, so disregard my previous vet message.

Here's what you can expect for your spatial learning when blocking GIRK4:

Furthermore, GIRK4-deficient mice performed similarly to wild-type controls in the passive avoidance paradigm, a test of aversive learning. GIRK4 knock-out mice did, however, exhibit impaired performance in the Morris water maze, a test of spatial learning and memory.
http://www.hvsimage.com/papers/PMID-%2010908597.htm

I think I'd rather have spatial learning problems than flutter or AF, esp. at this point in my life, as I feel I'm already neurotransmitter deficient.

This is quite complicated to understand all this information, but I'm trying.

Richard

Richard,

You're not kidding on the complexity comment.

Also, it seems to me that my short term memory has deteriorated just a bit while on disopyramide. This would be in agreement with the findings in your post.

PC

Richard,

Thank you for your continued support.

It all reminds me of the joke about three elderly gentlemen discussing their memory problems.

The first says "I sometimes find myself at the bottom of my stairs and I can't remember whether I've just come down or am about to go up".

The second says, "I know exactly what you're talking about. I sometimes find myself in front of my opened refrigerator and I can't remember whether I've just put something in or am about to take something out".

And finally the third says, "I don't know what the heck either of you are talking about, knock on wood".

(sound of rapping on wood)

(very brief pause)

Come in.

PC

PC,

That's the funniest joke I've heard in a while. The funnier thing is that I could relate to it. Actually, that's not too funny.

Richard

Dieter,

I found your questions and ponderings very intriguing. It put me on a search for different information, along with what PC has posted. In all the reading I've done, I have never come across what this article stated. Maybe it's been stated on this board before, and I just missed it:

"Sometimes, however, the SA Node fails. This can be a result of scarring, as can occur after a heart attack, or if the heart's conduction system is diseased. When this happens, one of the heart's "backup" pacemaker sites, called an ectopic focus, takes over. These ectopic foci may be located in the collecting or pumping chambers of the heart, or around the AV Junction (the junction between the atria and ventricles). The rate of these ectopic foci depends on their location.

When the SA Node fails, how does the heart decide which ectopic focus will take over? The fastest one always wins. This concept is known as overdrive suppression. The fastest focus effectively suppresses the activity of all other foci in the heart. This is a great design, when you think about it. Heart rates as slow as those generated by ectopic foci in the ventricles may exist normally in well-conditioned athletes at rest. Most of us, however, require faster heart rates to carry out our daily activities. That is why some people whose natural pacemakers have failed require an artificial pacemaker."

http://www.diagnosisheart.com/showarticle.php?articleid=129

I don't know if this is relevant to our situation, but it struck me strange when it stated "the fastest one always wins", and you stated "the fastest horse wins". Could the SA node be malfunctioning, or flickering per se, creating conflicting signals to the ectopic foci that thinks it should take over, creating a motion of irregularity?

Richard

Hello, Richard

Thanks for your comments. Yes - I have a feeling that a weakened SA node / conduction system may allow AF to happen, at least in certain cases. The weakening may have come about simply by advancing age, or it may be the result of some disease (not necessarily a heart disease) or some injury to the heart. A fully functioning and strong SA node / conduction system may simply nip any AF in the bud. See also my post today to James!

Regards,
Dieter

I thought you all might find this of interest, but I didn't have time to read it in its entirety.

Nitric oxide synthase is expressed in the sino-atrial node and animal data suggests a direct role for nitric oxide on pacemaker activity. Study of this mechanism in intact humans is complicated by both reflex and direct effects of nitric oxide on cardiac autonomic control. Thus, we have studied the direct effects of nitric oxide on heart rate in human cardiac transplant recipients who possess a denervated donor heart. In nine patients, the chronotropic effects of systemic injection of the nitric oxide synthase inhibitor NG-monomethyl-L-arginine (L-NMMA) (3 mg kg-1) or increasing bolus doses of the nitric oxide donor, sodium nitroprusside (SNP), were studied. Injection of L-NMMA increased mean arterial pressure by 17 ± 2 mmHg (mean ± S.E.M.; $P < 0.001$) and also had a significant negative chronotropic effect, lengthening the R-R interval by 54 ± 8 ms ($P < 0.001$). This bradycardia was not reflex in origin since injection of the non-NO-dependent vasoconstrictor, phenylephrine (100 µg) achieved a similar rise in mean arterial pressure (18 ± 3 mmHg; $P < 0.001$) but failed to change R-R interval duration (R-R = -3 ± 4 ms). Furthermore, no change in levels of circulating adrenaline was observed with L-NMMA. Conversely, injection of sodium nitroprusside resulted in a positive chronotropic effect with a dose-dependent shortening of R-R interval duration, peak R-R = -25 ± 8 ms with 130 µg ($P < 0.01$). These findings indicate that nitric oxide exerts a tonic, direct, positive chronotropic influence on the denervated human heart. This is consistent with the results of animal experiments showing that nitric oxide exerts a facilitatory influence on pacemaking currents in the sino-atrial node.
http://www.jphysiol.org/cgi/content/full/541/2/645

Richard

Hi, Richard

I forgot to mention that I know the reference you quoted. It is one that seems to support my view. If you can dig up anything in a similar vein, please do let me know - thanks!

Regards,
Dieter

In an earlier post on this thread I speculated that the natural selection pressures that allowed this possible IKACh polymorphism (undesirable) to persist over the many thousands since this mutation first appeared might lie in some conferred protection against the development of diabetes. Fran once said that she thought LAF was kind of anti-diabetes.

Accordingly I've been rooting around on the Internet looking at this from the standpoint of insulin sensitivity. Most of the current medical research is aimed at the larger problem of diabetes (v. LAF) and, therefore, tends to look only at insulin resistance. But I believe LAFers can also directly benefit from this research, if one works "backwards".

I would like to at least suggest a specific molecular explanation for this LAF/hypoglycemia connection that fits nicely with the polymorphism approach to explaining LAF.

To set the stage let me quote from
http://info.med.yale.edu/intmed/nephrol/pages/Desir.html
"We are currently examining the role of the voltage-gated K channel, Kv1.3, in renal K secretion and glucose metabolism. To that end, we generated a knockout mouse for Kv1.3 and discovered that the channel is an important regulator of insulin sensitivity and skeletal muscle glucose uptake."

At this site
http://westernphar.web101.discountasp.net/Vol43/pwps43_033.pdf
is an article that describes the rapid insulin sensitivity test (RIST). This is a measure of how much infused glucose is required in order to maintain normal blood levels for 30 minutes after injection of a certain amount of insulin. A larger amount of such glucose indicates incr4eased insulin sensitivity and a lower amount indicates decreased insulin

sensitivity or insulin resistance. About 60% of the infused glucose is controlled by hepatic insulin sensitizing substance (HISS). In other words HISS potentiates the insulin induced uptake of glucose by skeletal muscle. Hepatic parasympathetic nerve action, in conjunction with insulin, leads to release of HISS from the liver. This is inhibited by blockade of hepatic muscarinic receptors or blockade of hepatic nitric oxide synthase.

Given the apparent close linkage between hypoglycemia and LAF (26% documented in Hans' survey) and given the role of the inwardly rectifying potassium channel IKACh in the heart (controlled by the M2 muscarinic receptors of the vagus nerve) in triggering VMAF, could HISS be the missing link in establishing the connection at the molecular level? Could the muscarinic receptors in the liver be similar to their brothers in the heart? Could HISS be increased in VMAFers? Could it be increased via the same mechanism that it is increased in the heart, i.e., greater vagal tone? Could both be due to the same IKACh polymorphism? And why are NO and muscarinic receptors so closely connected?

PC v54

I'm really intrigued with the discussion by PC about physiologic rate adaptation, the inwardly rectifying potassium channel IKACh, hypoglycemia, HISS and AF. NO keeps on cropping up again and again too.

PC, are you saying:
1. That excessive i.e. UNCHECKED HISS production causes hypoglycemia?;
2. That this unchecked HISS production is down to the same kind of channelopathy (albeit in the liver) as is being argued as being the principal cause of AF in the heart - and both are REVEALED by - as opposed to caused per se by - high vagal tone?;
3. That the problem channelopathy in the liver is that the necessary blockade of hepatic muscarinic receptors is not taking place as is required (to reduce HISS levels) and furthermore that satisfactory synthesis of nitric oxide (again to reduce HISS) is not taking place?
4. Just like a lack of blockade of hepatic muscarinic receptors in the liver causes hypoglycemia, does a lack of blockade of the muscarinic receptors in the heart precipitate AF?
5. Is the lack of NO production also down to the IKACh channelopathy?
6. What is the nature of the problem with the IKAHc channelopathy? Is it as suggested in 4. above? Is the problem that too much or too little K gets through, that the flow is disrupted in such a way as to prevent satisfactory physiologic rate adaptation..... by not being 'quick'/'flexible' enough as second-second requirements change? (I suppose it is in reality MUCH more complex than this? But if it is, then RSD1235, tarantula venom, and scorpion venom cannot merely have a simple fixative effect?

Intriguing stuff, and I hope that PC doesn't mind my questions (-: Whilst I know I am no dummy, I do nevertheless struggle a little as regards 'seeing' the basic ideas through the medical terminology. If simple answers to the above questions help others to grasp the gist of the discussion then all to the good.

Channelopathies certainly offer one possible explanation why Erling and Fran have been able to eliminate their AF by following rigorous dietary approaches with the emphasis (fervently intended in Erling's case) being upon promoting the health of their cardiac myocytes' membranes.

Mike F.

Another thought upon (anxiously, as ever, in case of dumb-ass remarks or Qs!), re-reading my above posting, as regards seeking an answer to my question: "6. What is the nature of the problem with the IKAHc channelopathy?"

Is the answer that the inwardly rectifying potassium channel IKACh isn't errr inwardly rectifying?? In what way is it not inwardly rectifying ought accordingly to be my question. I assume that the problem is that the channel is not allowing the necessary maintenance of the gradient of K both inside and outside the cell???

Mike F.

Mike,

I think you understand exactly what I'm proposing very well.

The only point I'm at issue is #5. I don't know how NO and Kir channels might be connected. Perhaps Richard will dig up the connection.

Vagal tone directly controls AERP. When vagal tone is excessive, the lengthened AERP causes “loss of the physiologic rate adaptation".
"Increased parasympathetic tone will shorten the atrial refractory period through opening of the acetylcholine-dependent potassium channels (IkAch)."
http://www.ub.rug.nl/eldoc/dis/medicine/r.g.tieleman/c2.pdf

I must confess that I don't quite understand exactly how this works wrt depolarization/repolarization, etc.

I guess the best approach is to look at muscarinic gated K channels as a black box that is directly responsible for vagal tone and with it increased AERP (“loss of the physiologic rate adaptation” and LAF) and hepatic HISS release (hypoglycemia). It is also important to remember that this is all a hot area of research and one article’s Kir 1.x may be another’s Kir 1.y at this point in time.

The next question is: In taking a vagolytic to “muzzle” my muscarinic receptors and thereby lengthen AERP am I accelerating the aging process due to increased insulin by “muzzling” my HISS. Please visit
http://www.mercola.com/2001/jul/14/insulin.htm
Go the end of the article for an excellent discussion of the insulin and aging connection.

PC v54

Well, you certainly got my wheels turning again. I'm sure you all know this particular site, but it's more based on studies for HIV, with a lot of other ones thrown in. You'll have to bear with me however, because when I entered a search on nitric oxide, 17 pages came up. Of course I got side tracked a bit, but the information was astounding, at least to me. I'm only on pg. 5, and have accumulated enough for this post. The first link is the main site where I left off, but you can enter in the search field, whatever your little fibrillating heart desires, and see where it takes you.

http://www.aegis.com/search/Default.asp?QU=nitric+oxide&SCOPE=%2F&Page=5&Action=Search

Abstract: Formula-fed babies contract gastroenteritis more than breast-fed babies, which is of concern to mothers who cannot breastfeed or, as with HIV-infected mothers, are discouraged from breastfeeding. The ability of endogenous breastmilk xanthine oxidase to generate the antimicrobial radical nitric oxide has been measured and its influence on the growth of Escherichia coli and Salmonella enteritides examined. Breastmilk, but not formula feed, generated nitric oxide. Xanthine oxidase activity substantially inhibited the growth of both bacteria. An important natural antibiotic system is missing in formula feeds; the addition of xanthine oxidase may improve formula for use when breastfeeding is not a safe option.
http://www.aegis.com/aidsline/2000/dec/a00c0144.html
I found this study to be important, in how it relates to me. Remember I was low in Mo, which is an important element for xanthine oxidase. Could this have been my problem with digestion?

These results suggest that antibody efficacy in mice requires NO and support a role for NO in the regulation of pulmonary inflammation.
http://www.aegis.com/aidsline/2000/jul/a0070790.html

The redox pathway of S-nitrosoglutathione, glutathione and nitric oxide in cell to neuron communications.
http://www.aegis.com/aidsline/2000/may/a0051938.html

NO plays a role in mediating neurotoxicity associated with a variety of neurologic disorders, including stroke,

Parkinson's disease, and HIV dementia.
http://www.aegis.com/aidsline/1999/jun/a9960688.html

Regardless of the mechanism, a wide array of cardiovascular disorders characterized by endothelial dysfunction are reversible by L-arginine.
http://www.aegis.com/pubs/medline/1998/jan/m9814881.html

Chronic exogenous hyperinsulinemia in pregnancy: a rat model of pregnancy-induced hypertension.
http://www.aegis.com/pubs/medline/1998/jan/m9817058.html

Comparison of the effects of nitric oxide synthase inhibition and guanylate cyclase inhibition on vascular contraction in vitro and in vivo in the rat.
http://www.aegis.com/pubs/medline/1998/jan/m9819119.html

Contribution of nitric oxide to the acute antihypertensive effect of blockers of AT1 angiotensin receptors in spontaneously hypertensive rats.
http://www.aegis.com/pubs/medline/1998/jan/m9818749.html

Inhibitors of nitric oxide synthesis and ischemia/reperfusion attenuate coronary vasodilator response to pinacidil in isolated rat heart.
http://www.aegis.com/pubs/medline/1998/jan/m9812738.html

Ionic mechanisms of the effect of adenosine on single rabbit atrioventricular node myocytes.
http://www.aegis.com/pubs/medline/1998/jan/m9813059.html

Is glandular formation of nitric oxide a prerequisite for muscarinic secretion of fructose in the guinea-pig seminal vesicle?
http://www.aegis.com/pubs/medline/1998/jan/m9813592.html

Modulation of glutamate release from rat hippocampal synaptosomes by nitric oxide.
http://www.aegis.com/pubs/medline/1998/jan/m9815240.html

Nitric oxide and peroxynitrite affect differently acetylcholine release, choline acetyltransferase activity, synthesis, and compartmentation of newly formed acetylcholine in Torpedo marmorata synaptosomes.
http://www.aegis.com/pubs/medline/1998/jan/m9815239.html

Nitric oxide regulation of atrioventricular node excitability.
These results demonstrate that endogenous nitric oxide is involved in the muscarinic cholinergic attenuation of ICa-L in AV nodal cells; the mechanism likely involves the cGMP-stimulated phosphodiesterase.
http://www.aegis.com/pubs/medline/1998/jan/m9813057.html

It is postulated that diminished availability of tetrahydrobiopterin may additionally impair the generation of nitric oxide in atherosclerosis.
http://www.aegis.com/pubs/medline/1998/jan/m9812742.html

Organization and transmitter specificity of medullary neurons activated by sustained hypertension: implications for understanding baroreceptor reflex circuitry.
http://www.aegis.com/pubs/medline/1998/jan/m9818500.html

So I know this wasn't all relevant, PC, but after I knocked on wood, and then answered the door, I asked the man, "Why was I there?".

Richard

I'm getting really confused about the role of NO and AF. I get the impression that many are thinking it will help.... I am going out on a limb here. It would seem to me that NO has been produced in excessive amounts in those of us with AF. At least in me. Could excessive NO when it becomes a free radical be untraceable in the body when looking for straight unoxidised NO?

From this site http://www.medinox.com/medtek/faq/faq2.htm

"Free radicals are reactive, unstable and can cause cellular damage that leads to the pathology of strokes, heart disease, and numerous other illnesses. Unlike other free radicals, NO has both life-saving and life-taking properties. In small amounts, NO plays vital roles in many body functions including regulating blood pressure, establishing memory, and fighting pathogens. During inflammatory diseases and other disorders, NO is produced in excessive amounts and exhibits its free radical properties by injuring tissue and contributing to disease pathology."

Nitric oxide plays many important roles in the body. Under normal conditions, NO is produced in very small amounts which play crucial roles in regulating blood pressure, facilitating memory, and defending the body against pathogens. The body has natural protective mechanisms to protect itself from NO. Under pathological conditions, NO is produced in excessive amounts which can overwhelm these protective mechanisms. Excessive NO can then cause inappropriate enzyme activation and oxidative damage to vital cellular systems. Excessive NO production occurs during inflammatory conditions and is associated with numerous and diverse human diseases and disorders including intradialytic hypotension, diabetes, septic and hemorrhagic shock, stroke, allograft rejection, and Alzheimer's and Parkinson's diseases.

Nitric oxide (NO) consists of one nitrogen atom and one oxygen atom. In contrast, nitrous oxide has two nitrogen atoms and one oxygen atom. Nitrous oxide, commonly known as "laughing gas", is an anesthetic. In addition, nitrous oxide has very different chemical properties compared to nitric oxide. Nitrous oxide is not a free radical nor is it produced in the body. "

It would also seem that NO's connection with MSG would indicate excessive levels of NO in free glutamate sensitive people. http://www.immunesupport.com/library/showarticle.cfm/ID/4350/e/1/T/CFIDS_FM/

Fibromyalgia, Excessive Nitric Oxide/Peroxynitrite and Excessive NMDA Activity

"Excessive NMDA activity is implicated in FM by three different types of studies. The most recent of these was recently reported by Smith et al (2), reporting that a subgroup of FM patients had a complete resolution of their symptoms by removing both monosodium glutamate (MSG) and aspartame from their diets. MSG and aspartame are both described as excitotoxins (2), because both glutamate from MSG and aspartate from aspartame, activate the NMDA receptors in the nervous system and may lead to neural damage as a consequence of excessive activation. A major mechanism of such NMDA-mediated damage is produced by the excessive nitric oxide and peroxynitrite produced by such activation".

I know people say nitrous oxide is good - but for me it is anything but. In labour I threw it away in disgust after the first breath.

Sorry if I have picked this up wrong but I think NO is part of the problem and in the main caused by excessive free glutamate, I do not see it as the cure. It may have short term band aid for symptoms but no no no.....

Fran

PC
Again for my own situation your theory hits the nail on the head. Could my past hepatitis have changed the way my liver functions. I suspect strongly it must have changed it in some way. I had hep B a couple of years before the onset of AF. At some point in between I was hospitalised as I had gone yellow again. They said it was not Hep B this time and I got over it. Was this the hep C (as it had not been named at this time) that I created antibodies too. And hence why I went onto develop AF and seizures - the pregnancy and bad diet especially for two exacerbating the symptoms.

Anyway, found this article and thought it looked quite promising though I have yet to understand it all yet. The whole article is on line.

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=155044

Abstract
Recent evidence suggests the existence of a hepatoportal vein glucose sensor, whose activation leads to enhanced glucose use in skeletal muscle, heart, and brown adipose tissue. The mechanism leading to this increase in whole body glucose clearance is not known, but previous data suggest that it is insulin independent. Here, we sought to further determine the portal sensor signaling pathway by selectively evaluating its dependence on muscle GLUT4, insulin receptor, and the evolutionarily conserved sensor of metabolic stress, AMP-activated protein kinase (AMPK). We demonstrate that the increase in muscle glucose use was suppressed in mice lacking the expression of GLUT4 in the organ muscle. In contrast, glucose use was stimulated normally in mice with muscle-specific inactivation of the insulin receptor gene, confirming independence from insulin-signaling pathways. Most importantly, the muscle glucose use in response to activation of the hepatoportal vein glucose sensor was completely dependent on the activity of AMPK, because enhanced hexose disposal was prevented by expression of a dominant negative AMPK in muscle. These data demonstrate that the portal sensor induces glucose use and development of hypoglycemia independently of insulin action, but by a mechanism that requires activation of the AMPK and the presence of GLUT4.

And here is a reference to MSG and GLUT4

http://obesity-3.viagenbio.com/obesity-research-abs.2412.html

GLUT4 protein is differently modulated during development of obesity in monosodium glutamate-treated mice. Life Sci. 2002 Sep 6;71(16):1917-28. PMID: 12175706 [PubMed - indexed for MEDLINE]

Fran

I've been digging, and so far this is what I've found.

Cholinergic modulation of sinoatrial node pacemaking currents. Stimulation of the right vagus nerve leads to the release of acetylcholine (ACh), which binds to muscarinic M2 receptors on sinoatrial node pacemaking cells. This decreases the rate of spontaneous action potential generation by direct G protein (Gk) gating of an inward-rectifying potassium current (IKACh) as well as G protein (Gi) inhibition of adenylyl cyclase (AC) to decrease cAMP-dependent stimulation of the hyperpolarization-activated current (If) and cAMP- and protein kinase A (PKA)-dependent phosphorylation of the L-type calcium current (ICaL). M2 receptor stimulation may also activate endothelial NOS (NOS III), which increases cGMP levels via nitric oxide (NO)-dependent stimulation of soluble guanylyl cyclase (sGC). This may inhibit ICaL or If in the presence of high levels of ß1-adrenergic receptor stimulation via cGMP-dependent stimulation of phosphodiesterase (PDE) 2 and a decrease in cAMP, although this is controversial.

http://nips.physiology.org/cgi/content/full/17/5/202

*Novel Interaction between the M4 Muscarinic Acetylcholine Receptor and Elongation Factor 1A2**
http://www.jbc.org/cgi/content/abstract/277/32/29268

This is in pdf form, but I found it very interesting.
http://jap.physiology.org/cgi/reprint/84/5/1596.pdf

Richard

Dieter,

From ACC 52nd Session comes a slightly different perspective which you can read more of if you search on it:

What's New in Catheter Ablation for Atrial Fibrillation? Lessons Learned From the American College of Cardiology 52nd Annual Scientific Session
Cynthia M. Tracy, MD

The ability to successfully interrupt cardiac arrhythmias by catheter ablation is dependent on an understanding of the anatomy and physiology required for the arrhythmia to occur. There are 2 proposed mechanisms responsible for AF: focal activation and multiple wavelet reentry. In the former, a focus, typically located in one of the pulmonary veins, is felt to be the local trigger for the development of AF. Haissaguerre and colleagues[3] first reported the rapid firing of foci in or near the pulmonary veins leading to AF. These foci recruit the rest of the atrial tissue, and AF is perpetuated. While the pulmonary veins are the most common sites of origin of focal triggers, the superior vena cava and the coronary sinus can be other areas of triggers.

An alternative explanation for AF was originally described by Moe and is termed the multiple wavelet theory.[4] Here, it is postulated that multiple wavelets of atrial activation occur. These wavelets collide and coalesce through reentry in the atrial tissue and ultimately result in a global arrhythmia. Approximately 6 wavelets are required, and perpetuation of the AF is dependent on the conduction velocity and refractory period of the atrial tissue involved. As AF persists, functional and anatomic changes occur in the atrium, making the arrhythmia even more likely to continue. It was this model that led to the surgical procedures for AF. These procedures were designed to compartmentalize the atrium to prevent the wavelets from coalescing. Early success rates were modest, and recreation of the linear lesions formed by the surgeon during surgical treatment of AF was attempted using catheters. This and the growing recognition of focal triggers as the source of AF in many patients led to more locally directed procedures.

==========
And more towards the wavelet theory is this from Duke University:

In 1962, Moe proposed a ``multiple wavelet'' hypothesis which postulated the stability of AF was dependent on the continuous propagation of various individual wavelets in the atria. In other words, without a critical number of wavelets circulating in the atria, AF cannot sustain itself. This hypothesis was experimentally supported by Allessie et al., with mapping studies of acetylcholine-induced AF in isolated canine hearts. These two classic studies not only provided significant insights to the electrophysiologic state of the atria during fibrillation, but also raised some important questions about the controlling factors of these problematic wavelets. For example, the trigger, substrate and modifying factors of these wavelets need to be fully understood before an effective strategy, either for prevention of AF or atrial defibrillation can be designed.

One of the possible triggers of AF is ectopic impulses or atrial premature beats (APBs) originating from the atria or the atrioventricular junction. Note that it is common for APBs to occur in a normal individual, and the existence of extra nodal pacemakers (i.e. other than the sinus node) is not unusual. Therefore, the occurrence of APBs alone may not lend itself to AF development without a suitable substrate. An environment that allows an APB to initiate wandering wavelets and supports these wavelets' propagation is needed to sustain AF.

In addition to his multiple wavelet hypothesis, Moe also proposed several factors which could be important in sustaining wavelet propagation and creating a suitable substrate for AF perpetuation. A sufficiently large atrial mass, a relatively brief refractory period, a relatively slow conduction velocity, a temporal or spatial (anisotropy) dispersion of refractory periods are some of the suggested factors. It has long been recognized that a critical atrial mass is required to support a sufficient number of wavelets to sustain AF. A refractory period that is too short, and/or a conduction velocity that is too slow increase the probability that a tissue is ``re-excitable'' by an ectopic impulse, causing abnormal activation and impulse propagation of the atria. Wiener and Rosenblueth defined wavelength as the distance traveled by the depolarization wave during the duration of the refractory period, which is the product of conduction velocity and refractory period. It has been shown experimentally that if the wavelength is relatively long during fibrillation, fewer waves can circulate through the atria and fibrillation tends to self-terminate. Conversely, if the wavelength is short, a greater number of wavelets can be present and fibrillation tends to self-sustain. Although this experimental finding demonstrates the importance of wavelength in AF sustainability, it does not fully explain the formation of wavelets or reentrant circuits that cause AF.

One of the physical factors that cause the formation of reentrant circuits is conduction block. It has been demonstrated

that when the wavelength is short compared to the arc of a conduction block, the likelihood of setting up a reentrant circuit increases. A conduction block can be anatomical or functional in nature, i.e. caused by the heterogeneity of structural and/or electrophysiological properties. Temporal dispersion and anisotropy of refractory periods for example, are thought to play a major role in the formation of reentrant circuits. Once a suitable substrate is established, AF can be triggered by APBs and reentrant circuits can be formed. One of the problematic characteristics of AF is its progressive nature and gradual worsening with time. In other words, once AF is initiated, it modifies the atrial tissue in a way that further facilitates AF stabilization, a process called ``remodeling''. The electrical remodeling process starts within the first hours of AF with continuous shortening of atrial refractoriness. Such electrical remodeling process is found to be complete within 3 to 5 days in a goat model. Fortunately, this electrical remodeling process is completely reversible (within 2 days in the same goat model) once sinus rhythm is re-established and maintained. However, the longer the atria stays in fibrillation, the less likely that it will self-terminate. Also, if AF continues to sustain, further contractile and structural remodeling of the atria occurs, which requires a much longer time to fully recover.
==========
So there are various takes on the mechanism behind AF starting and ending and it's no surprise that we can be confused. My EP studied wavelet theory and made measurements in dogs during his fellowship. He observed that various conditions changed the number of wavelets to sustain AF so concludes the number 6 wavelets in humans is really variable. I personally don't even fathom how reentrant circuits can actually work and I've been ablated for flutter!

-Anton

Here's a bit more digging, and this one really peaked my interest, as it pertains to Glutathione.

Hepatic glutathione and nitric oxide are critical for hepatic insulin-sensitizing substance action

We tested the hypothesis that hepatic nitric oxide (NO) and glutathione (GSH) are involved in the synthesis of a putative hormone referred to as hepatic insulin-sensitizing substance HISS. Insulin action was assessed in Wistar rats using the rapid insulin sensitivity test (RIST). Blockade of hepatic NO synthesis with NG-nitro-L-arginine methyl ester (L-NAME, 1.0 mg/kg intraportal) decreased insulin sensitivity by 45.1 ± 2.1% compared with control (from 287.3 ± 18.1 to 155.3 ± 10.1 mg glucose/kg, P < 0.05). Insulin sensitivity was restored to 321.7 ± 44.7 mg glucose/kg after administration of an NO donor, intraportal SIN-1 (5 mg/kg), which promotes GSH nitrosation, but not after intraportal sodium nitroprusside (20 nmol · kg1 · min1), which does not nitrosate GSH. We depleted hepatic GSH using the GSH synthesis inhibitor l-buthionine-[S,R]-sulfoximine (BSO, 2 mmol/kg body wt ip for 20 days), which reduced insulin sensitivity by 39.1%. Insulin sensitivity after L-NAME was not significantly different between BSO- and sham-treated animals. SIN-1 did not reverse the insulin resistance induced by L-NAME in the BSO-treated group. These results support our hypothesis that NO and GSH are essential for insulin action.

http://ajpgi.physiology.org/cgi/content/abstract/284/4/G588

Richard

Anton,

Thank you for providing these two articles with excellent review and explanations of a complex topic.

PC

Another thought just struck me...

one of the situations I go into AF is resting after exercise.
(see http://james.dialsolutions.com/public/afterexercise.gif)

Is the sinus node just acting like a rapid focal ectopic site in this situation? (if you look at the graph there is no evidence of ectopics preceding the AF) i.e. my vagal tone is increasing as my heart slows down (which increases dispersion of

refractoriness) but the underlying rate is still so high that it's enough to kick the heart into AF.(the trigger to AF is a rapidly firing SA node rather than any rogue site)

Extending the speculation further, do some folk who think they have adrenergic AF because they go into AF when they are active have the same problem? (The background rate is high enough to act like a fast firing focal site but it's still vagal tone contributing to poor dispersion that sustains the AF?)

Hans, in your surveys have you ever asked the question if people feel ectopics before going into AF? I'd be interested to know if this is reported more often in the people who believe they have vagal AF.

All the best
--
James D

James,

Very good questions.

What is your HRV after the workout as you're going into AF?

I certainly agree that a higher HR would require less vagal tone to trigger AF, but how are you eliminating a rogue site. The increased automaticity due to catecholamines from a recent workout might trigger a rogue site into repeated and continuous firing (v. the increased but distinct PACs preceding the usual bedtime episode), although I doubt it. That's why I think HRV at the time is an interesting parameter. The HRV from SA node originating impulses without ectopics (in your case) should be much more steady.

I find that postworkout episodes are usually about an hour later and are more associated with an upper body workout. Catecholamines from the workout should be long gone. I've tried lying down immediately after a strenuous workout and have watched my HR plummet rapidly. The PACs for me don't come until HR has dropped to way below 100 bpm.

I think such workouts stimulate even more vagolysis in the baroreceptors and the vagotonic rebound is commensurately stronger (v. the usual lower body aerobic workout). This would be exactly the opposite of an astronaut returning to earth (vagolytic) from a weightless environment (vagotonic).

I have recently triggered a postworkout episode of tachycardia while on disopyramide. The absence of sufficient vagal tone prevented development of AF, but I'm still at a loss as to how to explain what triggered the rogue site (or the SA node) in the first place.

I personally think there are often other factors at play, e.g., dehydration, hypoglycemia, that complicate the picture. But what do I know?

PC

Time for another long post in the hopes of reviving the exchange.

It seems to me that we are gradually developing a distinction between AF that originates from PACs upon a background of high vagal tone (shortened AERP with increased dispersion) and AF that originates from a rapidly continuously firing focus upon a background that also has a shortened AERP but less so. In the former a few PACs during a time of high vagal tone are enough to trigger AF with no further need of PACs to sustain it. In the latter “rapid pacing” by this “aberrant focus” continually supplies waves easily fractured by the “loss of the physiologic rate adaptation” (nonvagal shortening of the AERP, e.g., greater sympathetic tone, with nonvagal dispersion, e.g.., subclinical fibrosis).

I would like to repeat that these two mechanisms for triggering AF seem to mirror what is happening in vagally

mediated LAF and adrenergic LAF respectively. Both have inappropriate shortening of the AERP and “loss of the physiologic rate adaptation”.

This distinction is highlighted in the articles cited by Anton in his recent post as well as in the article I cited *“Pathophysiological Mechanisms of AF”*
http://www.ub.rug.nl/eldoc/dis/medicine/r.g.tieleman/c2.pdf

Dr. Xu, whose team first identified the gene responsible for familial AF, feels that most people with LAF, have a polymorphism. A polymorphism is usually defined as a small (subtle) MUTATION in a gene present in greater than 1% of the population, i.e., it is only slightly altered. This gene has to directly impact AERP (“loss of the physiologic rate adaptation”), which is aberrant in all LAFers.

I speculated that this polymorphism involves IKACh, since this is the most critical ion channel in controlling AERP. However, perhaps it is more instructive to look at all the ion channels that together determine AERP as a black box. One of these channels is not working quite right in LAFers. Who knows exactly which one it is? More importantly who cares? This small mutation should have been removed from the human gene pool over the eons by natural selection. However, it has persisted nonetheless. It certainly is enticing to think that it has persisted because it provides some protection against diabetes. This is suggested by the almost complete absence of this disease amongst LAFers, who instead seem to wrestle considerably more than the general population with hypoglycemia.

HISS (hepatic insulin sensitizing substance) has not actually been identified. However, its presence can be measured via RIST (rapid insulin sensitivity test). It, like AERP, is controlled by the parasympathetic nervous system. This appears to be via M1 muscarinic receptor sites in the liver. It seems only natural that this same polymorphism that subtly affects M2 muscarinic receptor sites in the heart under the control of the vagus might also affect the M1 muscarinic receptor sites in the liver also under the control of the vagus. This would then explain both the LAF and the hypoglycemia. Both would be due to enhanced vagal tone.

There are more than a hundred different K channels. It is well known that many of these Kirs are heteromultimeric. This means that they are composed of the same basic units but in different ratios. If just one of the basic units were faulty, then many different Kirs and perhaps all the muscarinic receptors could be subtly affected.

About a year ago I happened to exchange some heart math freeze framer tracings with Hans. Included in the exchange was one I took while attempting to modulate my HR with deep breathing. I was able to create a pretty good sine wave type curve of my HR wrt time. He expressed some surprise at this and even wondered whether I might have had some special training in meditation. Retrospectively, I wonder whether this may have represented nothing more than a manifestation of strong RSA (respiratory sinus arrhythmia). This is a normal physiologic relationship between breathing and HR. During inspiration the HR quickens and during expiration it slows slightly. This is again mediated by the vagus nerve through stretch receptors in the lung and the carotid sinus and muscarinic receptors in the SA node. Could this be just another manifestation of vagal tone due to a channelopathy common to all these sites?

For this and other reasons I’ve always considered myself to have vagally mediated AF, i.e., due to multiple reentrant wavelets (Moe). However, I’ve recently experienced some interesting results while on disopyramide, a strong vagolytic. It appears to have unmasked something else.

Its effect on me was/is decidedly vagolytic with complete absence of PACs. However, once in awhile I would develop AF after going to bed and the episode would often terminate in the early AM or shortly after arising. So I tweaked the regimen wrt dosages and timing (more in the PM). PM episodes disappeared. However, I noticed that I could still trigger an episode about five hours after eating Chinese food or sushi, both potent sources of free glutamate. That was easy to stop via simple avoidance, but I’m considering a future experiment in which I would take large doses of Vitamin B6, a required cofactor for glutamate decarboxylase, for several hours after eating Chinese food or sushi. The presumed enhanced clearance of glutamate might thwart the otherwise predictable episode.

And finally, I’ve also noticed that I would get occasional tachycardia without AF. However this was an unusual tachycardia. I noticed that HR bounced around between 110 and 120 on my polar HR monitor and my HRV was usually in the 15 to 20 millisecond range. Normally at this HR my HRV is 2 or 3 ms. So, I interpret this to mean that the source of the tachycardia is not the SA node and it is not even a reentry phenomenon, e.g., AVRT or AVNRT. These

should all cause a much more uniform HR with a low HRV. Accordingly, it seems to me that this tachycardia is originating in some ectopic focus.

A recent article appeared in the medical literature that might shed some light on this. I've even written to the author but have received no response after several weeks.
"Electrophysiological And Electrocardiographic Characteristics Of Focal Atrial Tachycardia Originating From The Pulmonary Veins: Acute And Long-Term Outcomes Of Radiofrequency Ablation." in Circulation. 2003 Oct 21;108(16):1968-75 at
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=14557361&dopt=Abstract

"Focal ablation resulted in a cure in 96% (27/28)."

Furthermore, "*Intermittent bursts of tachycardia are observed within multiple PVs during persistent AF in a majority of patients with persistent AF*."
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12139285&dopt=Abstract

So, I'm now thinking that a significant component of my AF may be due to focal activation. Similarly many of you may also have bursts of tachycardia during AF. The bottom line is that this appears to "almost always resolve with RFA". I have no doubt that many LAFers not quite sure to which camp they belong (vagal v. adrenergic) have a similar combination.

Although it would appear that RFA offers a 96% of cure in such cases, I for one are not leaping at the prospect. In one of today's posts on the BB by Pam a weblink was provided to an article that states, "If it (catheter based ablation) can be developed to the point where it can be applied safely and effectively, ablation is likely to become the treatment of choice for many patients with atrial fibrillation. Many expect it to reach this point within two or three years. The bottom line is this: within a few years the treatment options for atrial fibrillation will become greatly expanded, and it is likely that the widespread frustration with this arrhythmia will abate."
http://heartdisease.about.com/library/weekly/aa112200d.htm

PC ?v54 (I think)

PC,

I just read and re-read your link on the mechanisms of AF, and it is just beyond my comprehension at this time. I guess I need pictures of cells and ion gates to show me exactly what is happening. It's very frustrating.

I don't know of what importance this link is, but I found it very interesting on the parasympathetic/sympathetic systems in hibernating animals and the different hypotheses and results with removal of the vagus nerve.

http://jeb.biologists.org/cgi/reprint/198/4/931.pdf

As for you trying extra B6 for Glu toxicity, I think that's a great idea. I'm presently taking around 150mg spread out during the day; some regular B6, but mostly P5P.

It is quite interesting that you are experiencing bouts of tachycardia now. I, as you, wonder why that is.

I also read that if the SA node is malfunctioning, then flecainide should not be administered, so that must not be my problem.

I'm off to at least find out more about what pyridine is, from your link above. I could not find much of anything pertaining to HISS and Kir. There's not much out there on that, but I'll continue to search.

Richard

You all might find this interesting, in regards to muscarinic potentiation of GABA, and the receptor being gated by insulin signaling.

http://www.acsu.buffalo.edu/~zhenyan/JN+m1+GABA.pdf

Richard

Richard,

I think you've found the technical explanation for my recent decline in short term memory.

PC

PC,

I hope this isn't a repeat of any posts already submitted here, but when I'm reading all this info it starts running together. This is pretty extensive and regards much that you are discussing.

http://pharmrev.aspetjournals.org/cgi/content/full/50/4/723

Just in case this is significant:

B. Atrial Fibrillation

Atrial fibrillation, the most common arrhythmia in man, is characterized by a marked shortening of the action potential duration, effective refractory period of atria, and a decreased rate of atrial repolarization resulting in increased dispersion of refractoriness as well as changes in atrial conduction velocity (Zipes, 1997; Nattel, 1999). The development of atrial fibrillation can be triggered by rapidly discharging atrial foci (mainly from pulmonary veins) or degeneration of atrial flutter or atrial tachycardia into fibrillation (Chen et al., 1999b; Scheinman, 2000). Risk factors for atrial fibrillation include cardiac diseases such as congestive heart failure, valvular heart disease, and myocardial infarction (Ryder and Benjamin, 1999).

It has been shown that sustained atrial tachycardia causes changes in electrophysiological function to promote the occurrence and maintenance of atrial fibrillation, a process referred to as atrial electrophysiological remodeling (Morillo et al., 1995; Wijffels et al., 1995). Recent studies have revealed that changes in ion channel functions play important roles in atrial electrophysiological remodeling caused by atrial fibrillation. In the canine atrial fibrillation model induced by chronic atrial tachycardia (rapid pacing), isolated atrial myocytes showed significant reductions in L-type Ca2+ current and ITO densities, without changes in Kir2.1, hERG, KCNQ1-minK, Ca2+-dependent Cl current, or T-type Ca2+ currents (Yue et al., 1997). Consistent with this observation, reductions in mRNA levels for Kv4.3, the 1-subunit of L-type Ca2+ channels, and the -subunit of cardiac Na+ channels were noted with no changes in mRNA levels for delayed rectifier K+ channel Kir2.1 or the Na+/Ca2+ exchanger. Western blot analysis further confirmed a reduction in protein expression of Kv4.3 and Na+ channels, whereas that of the Na+/Ca2+ exchanger was unchanged (Yue et al., 1999; Li et al., 2000). More importantly and consistent with data from the canine atrial fibrillation model, significant reductions in ITO (encoded by Kv4.3) and ultrarapid delayed rectifier (IKur) (encoded by Kv1.5) as well as L-type Ca2+ current densities were observed in atrial myocytes isolated from patients in chronic atrial fibrillation. Furthermore, quantitative Western blot analysis revealed that the expression of Kv1.5 protein was reduced by >50% in both the left and the right atrial appendages of atrial fibrillation (Van Wagoner et al., 1997, 1999). Although abnormalities of K+ channels may be fundamentally implicated in atrial fibrillation, other factors such as structural changes (Li et al., 1999) or heterogeneous alterations in atrial sympathetic innervation (Jayachandran et al., 2000) may also play critical roles in other forms of atrial fibrillation.

http://pharmrev.aspetjournals.org/cgi/content/full/52/4/557?maxtoshow=&HITS=10&hits=10&RESULTFORMAT=&fullte

xt=atrial+fibrillation&searchid=1069465918882_26&stored_search=&FIRSTINDEX=0&sortspec=relevance&resourcetype=1&journalcode=pharmrev#SEC2_7

Richard

Just for info, the article
http://heartdisease.about.com/library/weekly/aa112200d.htm
appears to have been posted to that site on 11/21/2000 - Atrial fibrillation
see...
http://heartdisease.about.com/library/weekly/mprev00.htm

(but more likely the 22 of November 2000 if you reverse engineer the url :)

My guess is that many of us will be of the 'mixed' variety. In my own case I would say I'm more likely to go into AF from focal activation if my vagal tone is high.

I've always been a little uncomfortable about sticking ourselves in the adrenergic or vagal pigeon hole. Even though I believe vagal tone plays a big part in my AF I think there are many other pieces to this jigsaw.
The question is which piece/s do we have to fix to get rid of AF?

--
James D (definitely 34 :)

What is your HRV after the workout as you're going into AF?
Rlx was 5ms (as high as 50ms before the exercise but went to 5ms pretty much straight away and stayed there for the full 5 minute 'workout')

LF/HF (if you believe the polar software) was around 5.7 for the minute before AF

I certainly agree that a higher HR would require less vagal tone to trigger AF, but how are you eliminating a rogue site.
I can't eliminate this. I'm just suggesting that, given a substrate capable of sustaining AF couldn't a fast firing SA node trigger AF just as easily as a rogue site? It's the failure to disperse the rapid firing in a uniform way that is enough to put the heart into AF rather than the extra noise of a rogue site??

I personally think there are often other factors at play, e.g. dehydration, hypoglycemia, that complicate the picture.
Whilst this may be true for extended exercise the example I gave was only after 5 minutes on an exercise bike so I think, at least in this case, they're unlikely to play a big part.

--
James D

James

What was your RLX for the minute leading up to AF? If it was single digit ms, I'd join you in eliminating a rogue site for your episodes.

When and what did you eat before the workout?

Also, I don't think it takes much "dehydration" to tip the scales.

PC

A couple of thoughts about my own situation recently FWIW. For illustrative and comparative purposes.

1. I've had 2 shortish (3hrs) self-converting episodes lately - one 3 wks ago and one 6 wks ago - both 3 - 6 am. (Episode before these two was 11 months previous - also early am and self-converting but 5 hrs long.) Two things:
a) In the last 6 weeks I've noticed more ectopics when physically exerting myself - particularly anaerobically..... such as today wielding a sledgehammer in a quarry collecting fossils. Definitely more exertion ectopics this last 6 weeks than before. In general my ticker has felt twitchier this last 6 weeks. The ectopics I get during the day are typically quite strong and lumpy feeling..... distinctly unlike the ones I get during the early am..... read on....
2. I have noticed on several occasions during the last 6 weeks - and before to a lesser extent - when awaking during the early am (anxious dream/nightmare usually) that my HR has speeded up with HIGH HRV (very noticeably higher) and very 'soft' 'light-feeling' ectopics - the sort you can hardly feel unless you are feeling your pulse (in contrast to the daytime ones I mentioned above). IF I wake up in time, I can get up and have a brief walk about and drink of water, and things will settle down. I wonder if my episodes commence when I don't awake in time by virtue of a dream (either precipitating or arising as a result of the faster HR and higher HRV?).

SO I can definitely relate to PC's experience of increasing HRV prior to AF.

It almost feels to me in overall terms that my ticker frequently gets close to to AF both day and night..... lumpy quite uncomfortable ectopics and/or one or two runs of the same per day during the daytime, but my ANS and other factors don't typically allow deterioration into AF during the daytime. I get the impression that AF for me in the daytime would be quite unpleasantly symptomatic because of how heavy my daytime ectopics feel. It's at night when high vagal tone and low HRs prevail that conditions develop which can readily initiate AF - increase in HR and BIG increase in HRV plus some repeating very light feeling ectopics and bingo..... although the AF is usually quite slow and not very symptomatic at all.

So that's my ramble for today. Like I said FWIW. I would, of course, be most interested to receive any feedback and comparable experience of others here. I know it's a bit of a ramble, but who knows, my own perception (very finely tuned-in!) of my own ectopy and AF might help the thought processes of other folks here (-:

Mike F.

What was your RLX for the minute leading up to AF? If it was single digit ms, I'd join you in eliminating a rogue site for your episodes. It was 5ms.

When and what did you eat before the workout?
No idea, the graph is from 9th Jan 2003 and I don't keep a diet log. It happened at around 8pm - the most likely event would have been a very light snack around 6:00pm (I've been having my main meal at midday for a couple of years now).

Also, I don't think it takes much "dehydration" to tip the scales.
This wasn't anything I could describe as working up a sweat. I think if 5 minutes at a not hard pace on an exercise bike was enough to tip the scales I would have to have been seriously dehydrated before hand.
--
James D

James,

We truly are all different, but there's a common thread there somewhere.

PC

James,

Since your HRV at the onset of the AF episode was about 5 ms, indicating primarily adrenergic input, just what makes you think that the tachycardia was potentiated by vagal tone? You had very little vagal tone at the time.

Do you think vagal tone to the SA node and vagal tone to the rest of the atria are separate?

PC

James,

The nature of ectopic beats is covered in the latest survey results. See page 2 of the November 2003 issue of The AFIB Report.

Hans

PC, I'm not sure an Rlx or HRV analysis is going to pick up on the changes that go on from second to second. (The underlying statistics just don't alter quickly enough to give such a dynamic response- the best they can achieve is a trend). I'm sure if I hadn't gone into AF and was able to analyse the 5 minutes post exercise it would have indicated the switch from adrenergic to vagal predominance.

The point I was trying to get across was that my AF happens immediately after exercise on the slowing down phase where vagal tone is, I assume, starting to rise as the adrenergic side falls. Somewhere in this rise and fall there's enough vagal tone (I've no idea if it's just in the SA node or throughout the atria) to increase the dispersion of refractoriness to enable AF to persist but there is still sufficient adrenergic tone to produce a fast enough impulse to trigger the AF.

BOTH a trigger and a vulnerable substrate have to be present for AF to start and persist. The vast majority of my AFs start when my vagal tone is high, my heart rate is low and a rogue site starts some ectopics firing at a rapid enough pace to get the AF started. (I'm guessing it's a rogue site and my SA node is just going too slow to win the race)
I'm suggesting that post exercise the still relatively fast firing SA node takes place of these rogue ectopics that usually start my AF. (but only after there's been sufficient rise in vagal tone to mess with the substrate)

All of my AF that involve exercise start on the downslope of heart rate - there must be a good reason for this :)

Hans,
Thanks for the info, the November report is still sitting in my printer tray - I'll have to do some catching up!

--
James D

James,

Thanks for the response.

I understand what you're surmising. I just have a hard time seeing how an HRV of 5 ms "confirmed" by and compatible with the higher HR indicates sufficient vagal tone to produce the required "fertile soil" - even if there is a slight lag by

the Polar monitor in registering this change.

My HRV changes very quickly along with my HR after a workout. I've never gone into AF at an HRV of 5 ms. I've never gone into AF at a HR>80bpm/HRV<20 ms, although AF occurs most frequently when HR dipped below 50. But we're all different.

PC

Thanks for your thoughts PC, it is guess work on my part. I suppose knowing how much norepinephrine /acetylcholine is being squirted into the heart at any given instant is a bit hard to measure.

Has anyone read any info what the 'normal' relationship between the two sides is when coming down from exercise? I'd like to know at what rates the breaks get pressed (vagal tone increases) rather than slowing down by easing off the accelerator (adrenal).

Are there any conditions/situations where both sides are working hard? Which side wins control of underlying heart rate if this condition exists?

All the best
--
James D

In continuing my digging, I found these studies to be of interest:

Voltage-gated K+ currents in rat somatotrophs are increased by somatostatin (SRIF) through unidentified G protein. In this experiment, somatotroph-enriched cells (up to 85%) were obtained from ovine pituitary glands and further identified by the increase in K+ currents by SRIF. The whole cell recording was employed to study the voltage-gated K+ currents. A reversible increase in K+ currents (up to 150% of control) was obtained in response to local application of SRIF (10 nM) but not vehicle. When the guanosine 5'-O-(3-thiotriphosphate) was included in the pipette solution (200 µM), the recovery phase of K+ current response to SRIF was abolished. Inclusion of guanosine 5'-O-(2-thiodiphosphate) (200 µM) in pipette solution blocked the K+ current response to SRIF. Intracellular dialysis of antibodies against o-, i-, i-1-2-, or i-3-subunits of G proteins via patch pipettes was confirmed by immunofluorescent staining of the antibodies. Antibody dialysis alone did not modify voltage-gated K+ currents. Dialysis of anti-i or anti-i-3 antibodies significantly attenuated the increase in K+ currents that was obtained after application of 10 or 100 nM SRIF. Dialysis with anti-o, anti-i-1-2, or heat-inactivated (60°C for 10 min) anti-i antibodies did not diminish the effect of SRIF on K+ currents. We conclude that the Gi-3 protein mediates the effect of SRIF on voltage-gated K+ currents in ovine somatotrophs.

http://ajpendo.physiology.org/cgi/content/full/275/2/E278

Growth hormone-releasing hormone (GHRH) has been shown to stimulate growth hormone (GH) secretion in several species since it was identified more than a decade ago (Guillemin et al. 1982; Spiess et al. 1982; Heiman et al. 1984; Jansson et al. 1985). It is generally accepted that in somatotropes, GHRH increases Ca2+ influx via voltage-gated Ca2+ channels, and this leads to an increase in intracellular free Ca2+ concentration ([Ca2+]i) and subsequently to an increase in GH secretion (Lussier et al. 1991; Chen et al. 1993, 1994a; Naumov et al. 1994; Chen & Clarke, 1995a; Kwiecien et al. 1997). Activation of sodium currents by GHRH was reported in rat somatotropes (Kato & Sakuma, 1996, 1997), which was suggested to initiate membrane depolarisation. The main second-messenger system employed by GHRH is believed to be intracellular cAMP (Chen et al. 1994a, 1998; Sartin et al. 1996; Wu et al. 1996; Takei et al. 1996, 1998; Kato & Sakuma, 1997). Since most of the ionic currents across the membrane at the resting potential are carried by K+, the transmembrane K+ channels are thought to play an important role in GHRH-induced depolarisation (Mollard et al. 1988; Ohlsson & Lindstrom, 1989; Sikdar et al. 1989; Chen et al. 1993; Chen & Clarke, 1995a). GH-releasing peptide (GHRP), a synthetic GH secretagogue, has been shown to decrease the voltage-gated K+ currents in rat somatotropes (McGurk et al. 1993). GHRP also depolarises ovine somatotropes in a very similar way to that by GHRH (Chen & Clarke, 1995b). Somatostatin, a GH-release inhibitory factor, has the capacity to increase K+

currents in neurones (Yatani et al. 1987; Scheweizer et al. 1998) and the voltage-gated and inwardly rectifying K+ currents in rat, ovine and human somatotropes (Wang et al. 1989; Chen et al. 1990, 1994a; Sims et al. 1991; Takano et al. 1997; Bauer, 1998; Chen, 1998). GHRH may antagonise the inhibitory action of somatostatin partially by reducing K+ currents. This has raised the questions whether GHRH has the same effect on voltage-gated K+ currents in human somatotropes as that of GHRP in rat somatotropes, and what is the intracellular signalling pathway for such a possible reduction in K+ currents.

http://www.jphysiol.org/cgi/content/full/520/3/697

The Kir3.0 subfamily, designated as GIRK channels, regroups Kir channels that are gated by GTP binding proteins (G-proteins). These channels are expressed primarily in the brain and heart. The first member to have been cloned was GIRK1 (Kir3.1), which is predominantly expressed in the cardiac atrium (25) . It is a strong inward rectifier with a single channel conductance of ~42 pS. Coassembly of Kir3.1 (GIRK1) with Kir3.4 (GIRK4 or CIR) forms the receptor-gated Kir channel, also known as the KAch channel (32) . This channel helps to slow down heart rate during vagal stimulation of muscarinic M2 receptors through activation of ß subunits of the G-proteins (33 34 35 36) . This channel is also responsible for the bradycardic action of adenosine through activation of A1-adenosine receptors (35) . Knockout mice lacking GIRK4 are unable to adjust heart rate on a rapid time scale, indicating a critical role for KACh in the regulation of heart rate variability (37) . In the central nervous system, activation of GIRK channels is involved in the inhibitory actions of GABA, acetylcholine, adenosine, somatostatin, and opioid peptides. Mice lacking GIRK2 are more susceptible to develop seizures induced by GABA antagonists (38) .

http://www.fasebj.org/cgi/content/full/13/14/1901

Richard

Hans, et al - I'm thinking out loud here as a result of the post ablation requirement to take Lipitor to reduce inflammation in ablation area and promote healing without stenosis.

When I asked my discharge doc about the action of inflammation in that area and how the Lipitor was supposed to help, he commented that it reduced the amount of oxidized LDL in the blood cholesterol. It is thought the oxidation causes the inflammation. Healing without inflammation is found to reduce the chance of stenosis and to keep the heart cells calm and non-irritated while healing.

Therefore – Hans, I'm wondering if afibbers have in common, unfavorable levels of LDL or, additionally, C-Reactive Protein. I had previously asked several CCF cardiologists their opinion of elevated C-Reactive Protein (marker for inflammation) levels and was told they definitely feel there is a relationship between inflammation and afib… I posted the results of one CCF study regarding this.

My question was then and still is, which comes first – the irritation of the heart cells leading to afib which causes a rise in CRP, or elevated levels of CRP irritating heart cells enough to be a substrate for afib.

I also have a question about the hypotheses expressed here regarding the fast firing of the SA node , AV nodes, and rogue sites as triggers to afib…….. short of ablation, is there anything that can be done about this? Do we know what would act as a calming mechanism to the electrical system.

I choose my favorite – magnesium – since magnesium has been found to slow the release of both adrenaline and noradrenaline, and to partially block adrenergic receptors. An intractable magnesium deficiency could most certainly be a player in the mechanism for afib, since over 80% of the population is found to be deficient. It would seem like the place to begin keeping in mind that a few months of magnesium supplements does not reverse intractable magnesium deficiency. It's a whole study in itself.

Animal and clinical studies have shown that chronic magnesium depletion has direct consequences for both the heart and blood vessels. These include: Arrhythmias due to abnormal shifts of the mineral potassium into and out of heart cells and abnormal electrical activity in the heart shown by electrocardiogram results. (Seelig – The Magnesium

Factor).

These three possible factors – high LDL, high CRP, intractable magnesium deficiency should definitely be considered as causative in the cascade of events that lead to afib. The good news is each condition can be treated and corrected by relatively simplistic and inexpensive methods as opposed to ablation.

Jackie

Jackie,

Several studies have shown that afibbers tend to have higher CRP levels. However, I do not personally have a high CRP level nor have the LAF surveys confirmed this connection. Nevertheless, I do believe there is a connection between inflammation and afib and actually discussed that in some detail in the book (pages 130-137). I would think that the inflammation is the cause of the high CRP rather than the other way around. I do not know why Lipitor is prescribed after an ablation but would think it is more for its antiinflammatory properties than for its ability to lower LDL.

I doubt that afibbers, especially vagal ones, would tend to have high LDL levels, but it would be an interesting question in a future survey.

Hans

I've been pushing the K+ channelopathy approach to explaining LAF, at least for the vagally mediated variant. I've also been recommending spironolactone in an attempt to support serum K+ levels and recently read the following abstract. I thought that you might find it interesting. Long QT Syndrome is due to a potassium channelopathy. The spironolactone dose translates to over 200 mg for an adult.

A New Oral Therapy For Long QT Syndrome: Long-Term Oral Potassium Improves Repolarization In Patients With HERG Mutations
"The subjects ranged in age from 11 to 52 years. The average daily KCl and spironolactone dose was 3.3 ± 1.5 mEq/kg and 3.5 ± 1.2 mg/kg, respectively, and this regimen resulted in an increase in serum K+ from 4.0 ± 0.3 to 5.2 ± 0.3 mEq/l. There were no serious complications associated with therapy."

http://www.cardiosource.com/library/journals/journal/article/abstract?acronym=JAC&uid=PIIS0735109703011288&kwhighligh=

Also, wrt urinary magnesium wasting I've always felt that drinking an alkaline mineral water might result in loss of Mg along with HCO3- in the urine. The following comment from Dr. Sara Myhill, who uses IM Mg to treat Chronic Fatigue Syndrome (fibromyalgia) supports this view:
"Hyperventilation makes you lose magnesium in the urine. This is because hyperventilation induces a respiratory alkalosis, the body excretes out bicarbonate to compensate, but each bicarbonate is negatively charged and carries a positively charged cation with it – in this case magnesium."

http://www.immunesupport.com/library/showarticle.cfm/id/2892

So, if you are drinking waller water or other Mg laden mineral water you ought to seriously consider neutralizing it. I'm a real believer in waller water (aqueous Mg). According to Dr. Walt Stowall Mg deficiency in the general population (over 80% according to the Nat'l Academy of Sciences) has resulted in a virtual epidemic of muscle cramps, migraines and arrhythmias. I've struggled for years with nocturnal leg cramps (calf or foot). I've been drinking aqueous Mg for well over a year and only in the last 3 months have I become finally free of these leg cramps.

PC v54

Hans – I realize I came to the CR late and this session is completed but I wanted to comment on your last posted answer to me.

Most specifically, oxidized LDL is the culprit in inflammation at the site of the PVI and is specifically why the use of Lipitor is recommended by Dr. Natale post-ablation.

In my investigation of natural alternatives to Lipitor, I've found several references regarding the action of policosanol (the natural product derived from sugar cane wax) to lower cholesterol, lower LDL and raise HDL and without the burden of side effects such as liver toxicity, muscle weakness and cognitive dysfunction. This helps clarify for me the role of oxidized LDL and inflammation.

Following are just two excerpts of many excerpts from much data:

One of policosanol's important actions is to inhibit the oxidation of LDL.(4) Oxidized LDL is dangerous. It promotes the destruction of blood vessels by creating a chronic inflammatory response. Oxidized LDL can also provoke metalloproteinase enzymes.(5) These enzymes promote blood vessel destruction, partly by interfering with HDL's protective effect. Studies show that rats treated with policosanol have fewer foam cells, reflecting less inflammatory response causing less blood vessel destruction.(6,7)
http://www.smartbodyz.com/policosanol-HDL-LDL-cholesterol-Text1.htm

Byproducts of LDL oxidation are bioactive, and secrete inflammatory cytokines, growth factors and cell surface adhesion molecules. In response to these oxidative bi-products, smooth muscle cells proliferate in the wall of the artery, resulting in the narrowing of the lumen and eventual blockage. Oxidized LDL cholesterol can also inhibit the production of prostacyclin and nitric oxide, which act as vasodilators and inhibitors of platelet aggregation.

Policosanol is a mixture of essential alcohols isolated from sugar cane wax (13). The main constituents are octacosanol (66%), hexacosanol (7%), and triacontanol (12%). Eicosanol, tetracosanol, nonacosanol, dotriacontanol, tetratriacontanol and heptacosanol make up the remaining 15% of essential alcohols.

There is a significant body of evidence demonstrating the benefits of policosanol with respect to cardiovascular disease. In the mid to late nineties, one research group proposed that policosanol was able to reduce endothelial damage by inhibiting the production of foam cells (14, 15). Foam cells are macrophages that can migrate into the endothelium of the blood vessels and contribute to atherosclerotic plaque formation (2). Other researchers believe policosanol has a modulating effect on HMG-CoA reductase, the rate-controlling enzyme in cholesterol biosynthesis, but the precise mechanism remains unclear (16-18). Still, other investigators believe policosanol may inhibit cholesterol synthesis in the liver at a step before mevalonate production, but total inhibition of the HMG-CoA reductase is doubtful (13).

ØMore recent work suggests policosanol inhibits LDL cholesterol oxidation (19, 20). This was revealed when markers of peroxidation, such as thiobarbituric acid reactive substances (TBARS), and malondialdehyde (MDA) were lower in the cultures treated with policosanol.
Ø
Oxidation of LDL cholesterol has been linked to heart disease and was the recent cover story in Scientific American magazine (2). Bi-products of LDL oxidation are bioactive, and secrete inflammatory cytokines, growth factors and cell surface adhesion molecules.

ØIn response to these oxidative bi-products, smooth muscle cells proliferate in the wall of the artery, resulting in the narrowing of the lumen and eventual blockage. Oxidized LDL cholesterol can also inhibit the production of prostacyclin and nitric oxide, which act as vasodilators and inhibitors of platelet aggregation.
http://www.drhoffman.com/policosanol/

So – back to my original hypothesis – might not afib be triggered from the inflammatory effect (heart cell irritability) caused by oxidized LDL present in people who have unfavorable levels? I'm just backing into this from a reverse standpoint.

Incidentally, my LDL level has never been considered good. I will soon be tested after 6 months of treatment with

policosanol and will report any significant findings.

Now, on to Candida!

Jackie

Jackie,

I recently subscribed to the Health Alert newsletter on the recommendation of Dr. Mercola. The most recent issue contains an article about Lipitor and a study at the Cleveland Clinic. This is probably why Dr. Natale advocates Lipitor post ablation. But the study is a bit disturbing and can be read at
http://www.hsibaltimore.com/more.shtml

The study was underwritten by Pfizer, which makes Lipitor.

There was also a recent study showing that persistent AFers had a much longer AF free period post cardioversion, if Lipitor was given post cardioversion (v. controls). This is growing evidence of the mainstream medicine/statin love affair. Just be sure you take your CoQ10.

PC v54

PC - thanks for this information. I'm sure the CCF benefited someway from this study and probably has some agreement to push Lipitor.

I have no use for statins. I think they are dangerous drugs. My previous experience with earlier versions - Pravachol and Zocor - left me with severe muscle weakness which might even be considered permanent. My MD argued at the time there was no such side effect.

When was told I could be placed on Lipitor, I addressed all my concerns with Dr. Natale's group about this and was given it anyway. (one size fits all medicine). Well, sure enough, in about 3 days after the first dose, my legs were so weak and painful, I could hardly move around. By the end of a week, I called Michelle of the CCF to report in. She said cut the dose in half. The half dose did nothing to help the weakness and pain.

Before ablation, I inquired if they recommended supplementing with CoQ10 because of the depletion factor.....my answer was that they did not advise to take or not to take CoQ10.

So, while I was pleased to have the expertise of Dr. Natale, I'm a disconcerted because of an apparent lack of concern for me as a patient who apparently can't metabolize Lipitor and also because they fail to recognize the importance of CoQ10.

Previous to ablation, I had used policosanol for six months. PC has none of the side effects such as liver toxicity, muscle destruction or cognitive impairment.

I took myself off the Lipitor and am continuing with policosanol and stepping up all antioxidant supplements.

Since the CCF feels the oxidized LDL is the inflammatory factor at the ablation site, most likely the Lipitor does indeed cut down on the presence of LDL. Liptor is reported to be the strongest and fastest acting statin out there today so it makes sense to use it for this short period and for a targeted purpose.

I'm waiting to see my labs to determine if a baseline lipid profile was done before they calculated the dosage for me. I won't be surprised if a baseline was not done.

But the point of my post was - might not individuals with high LDL levels be more prone to have afib as a result of the inflammatory effect of the oxidized HDL?

I think it would be good to include on a survey - and if afibbers don't now their LDL levels they should be tested... and definitely along with the CRP and the Lp(a).

My CRP is just about 1.0 as I recall - and it should be as close to zero as possible....and my Lp(a) is in the normal range..... the only variable is the LDL which was higher than acceptable six months ago.

Thanks again for looking up the CCF/Lipitor connection.

Jackie

There is an interesting article at http://www.vitamincfoundation.org/EDTAPR081402.htm

Entitled *JAMA study proves Vitamin C and Magnesium benefits for cardiovascular patients.*

It touts the benefits of Vitamin C and magnesium over statins wrt prolonging "exercise time to ischemia". This is indeed noteworthy, given Jackie's post regarding Dr. Natale's rationale for post ablation Lipitor. This fits right in with Linus Pauling's theory regarding Vitamin C and cardiovascular disease. Although the cited study involved IV Vit C, its water solubility suggests that similar results could be obtained with oral administration.

Anyone with an elevated CRP should have an Lp(a) level determined.

Although run by an Aussie, you may find the following weblink helpful:

http://www.eternalhealth.org/mens_health/7new_theories.htm

PC v54
