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P cells and Free Radicals

By Patrick Chambers MD

P is for pole cells and they are the pacemaker cells of the heart. These have traditionally been described only in nodal tissue (SA node and AV node). However, in August of 2003 they were first described in human pulmonary veins (enter left atrium). Other subsequent reports have confirmed this. To date they have not been found in the vena cavae that enter the right atrium or anywhere else in the heart for that matter.

There have been numerous reports in the literature about the increasing success of catheter ablation via pulmonary vein isolation (PVI). Initially I thought that its success was due to transection of vagal nerve fibers that enter the left atrium via its pulmonary veins. The increase in HR post ablation certainly testifies to this event. However, vagal nerve fibers to the SA node travel along the superior vena cava (right atrium) and yet this doesn't seem to be a player in the PVI success story. Accordingly, I have become more interested and would like to share my research into the matter and hear your thoughts here in the CR.

Pacemaker cells are unique in that they slowly depolarize by themselves, hence their greater inherent automaticity. This is due to their unique Na and K ion channels.

Acetylcholine (ACh) released from the vagus nerve endings binds to muscarinic receptors on the pacemaker cells. ACh not only affects K channels but also a unique Na channel (AKA the funny current). In fact cardiac pacemaker activity is regulated by at least five different classes of ion channels and by the opposing influence of sympathetic and parasympathetic stimulation.

In September of 1998 the Bordeaux group published an EP study of 45 patients with frequent paroxysmal AF. They looked at the location of the triggering atrial ectopic beats and found that 94% were located in the PVs (2-4 cm inside the veins). I'm not sure what per cent of those with paroxysmal AF qualify as lone (LAF), but I would guess that if one accepts any degree of hypertension in the definition of LAF, it would be a majority.

In October of 2002 this same group published an EP study of 28 patients with paroxysmal AF (average age about 50) v. 20 age matched controls. They evaluated the effective refractory period (ERP) of cells in the pulmonary veins and the left atrium in both groups. They found that left atrial ERP did not differ between the two groups. However, in the AF group the PV ERPs (v. the LA ERPs) were shorter whereas in the control group they were longer. Furthermore, they found that there was greater dispersion of PV conduction velocity in the AF patients and that in these same patients AF was more easily induced (by fast pacing) in the PVs (22/90) than in the left atrium (1/81). Incidentally dispersion of conduction velocity is now believed to be more instrumental in the initiation of AF than dispersion of refractoriness. Consequently, these PV refractoriness and conduction properties create a substrate favorable for reentry.

It would appear to me that these PVs represent the oft quoted but elusive "defective substrate" of LAF. This is what is responsible for "the loss of physiologic rate adaptation" present in AF, i.e., conditions that should slow down the heart (slower conduction velocity, shortened refractory period) often result in a tachyarrhythmia instead.

Putting these two studies together paroxysmal AFers appear to have a problem with their PVs. It would seem logical to implicate P cells in this process. In December of 2003 there was a nice review article in the Journal of Cardiovascular Electrophysiology entitled "Basic Electrophysiology of the Pulmonary Veins and Their Role in Atrial Fibrillation: Precipitators, Perpetuators, and Perplexers", summarizing that state of affairs to date on paroxysmal AF. You can read it at

http://www.blackwell-synergy.com/links/doi/10.1046/j.1540-8167.2003.03445.x/full/?func=showHome#h1

but you might have to register first (it's free).

Recently it was mentioned in an article posted on the BB that the PVs not only initiate AF but also contribute to its maintenance. I can't remember who posted the article but Erling picked up on the tidbit. It appears that this venous tachycardia (AKA "PV bursting") emerges during AF but not in AF induced in normal hearts. This was a canine study. A majority of those with paroxysmal AF have this PV tachycardia during AF and it is much more often intermittent than continuous. In a recent sheep study this bursting was enhanced by increasing intraatrial pressure. This leads to the question of whether transition to chronic AF is more a function of atrial enlargement per se (ability to accommodate more wavelets) or to the increased intraatrial pressure caused by prolonged intermittent AF that causes that enlargement.

The changes in the ERP that are present in those with paroxysmal AF appear to be due to many ion channels (inward L-type Ca channels, several K channels and sodium channels). Initially many (inc me) have felt that a specific ion channelopathy was the culprit for LAF. A K channel polymorphism (a mutation present in more than 1% of the general population) seemed likely. However, given recent information, it would appear that it is not nearly that simple (what a surprise!). This simplistic view has also been responsible for my failure to completely embrace the inflammation/oxidative stress hypothesis in the genesis of LAF. I previously had thought that damage due to inflammation was far too broad to manifest only as a simple channelopathy without other evidence of heart disease (LAF).

Once convinced that oxidative damage is at the center of LAF one must decide how and why this happens to the P cells in the PVs v the SA and/or AV nodes. I think the answer lies in the relationship between the lungs and the left atrium. The former are a constant source of free radicals from cigarette smoke, allergens, ozone and just air pollution in general. These have been implicated in a long list of pulmonary diseases. Hans on pp. 137-138 in his book LAF: Towards a Cure has suggested that "high oxygen pressure and shear stress (present in the pulmonary veins) is a potent breeding ground for reactive oxygen species (ROS)". He further suggests that exercise might contribute to this. Whether the high association of LAF in endurance athletes is due to excess vagal tone or actual P cell damage has not yet been determined.

Free radicals attack cell membranes as well as nuclear and mitochondrial DNA. This general process is called oxidative stress. Membrane damage due to free radicals is called lipid peroxidation and this is felt to be the mechanism responsible for the well known development of AF after coronary artery bypass grafting (CABG) via ischemia/reperfusion damage. This is just a fancy way to describe what Hans is saying. Ion channel damage would loom large in the lipid peroxidation scenario.

Sometime last year I believe Richard posted on the BB an article written in December 2003 entitled Atrial Fibrillation: Are We Treating the Right Disease?

http://www.medscape.com/viewarticle/463648_print

That article presents lots of data linking redox state with arrhythmia. Redox is short for reduction/oxidation, which refers to the gain or loss respectively of electrons caused by free radicals. David van Wagoner of the Cleveland Clinic in an article written sometime after May 2002 addressed the issue of oxidative stress and AF. This can be viewed at

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

He points out that AF is associated with calcium overload, which can increase the production of free radicals. If you buy the oxidative stress hypothesis, then this explains the "AF begets AF" observation. Numerous studies have documented an inverse relationship between the levels of free radicals and their scavengers such as vitamins A, C, and E, magnesium and selenium. There are numerous studies touting the preventative effects of preoperative Mg and Vitamin C on the development of AF post CABG.

Furthermore, one can measure the cellular damage caused by oxidative stress through its biochemical markers. High sensitivity C reactive protein (hs CRP) would be at the top of this list. For years mainstream medicine has "shouted from the mountaintops" the dangers of cholesterol. The NIH spent millions of dollars trying (and failing) to show a relationship between dietary cholesterol and heart disease. High blood cholesterol, which is associated with heart disease, is largely genetically determined. But it is less important than an elevated CRP in predicting future heart disease. Although this is not exactly late breaking news, please visit

http://www.usatoday.com/news/health/2005-01-05-heart-inflame_x.htm

to read an article on this that appeared in a major newspaper today.

Having said all this, why doesn't everyone have AF? There are many cardiac ion channels. In fact there are several hundred K channels alone. IMHO there must be hundreds of polymorphisms yet to be discovered that involve P cell ion channels. If the mix of polymorphisms is right (or more appropriately, wrong) and sufficient cell membrane (and ion channel) damage due to free radicals has occurred, then AF will appear in these genetically predisposed individuals. IMHO don't hold your breath waiting for the announcement about some single genetic ion channelopathy that will explain the growing epidemic of LAF.

However, this mushrooming epidemic is due not only to the concomitant increase in environmental free radicals but also to the general decline in the quality of our food. We can no longer obtain the required antioxidants through diet alone. Mainstream medicine has again been slow to step up to the plate and recognize this fact. The pharmaceutical industry is in large part responsible for this. Better to take a pill for what ails you. But the general public is not blameless in this affair. Most patients don't want to be told to lose weight, stop smoking and eat their fruits and veggies. "Just gimme a pill doc." And if he doesn't they'll find one that will.

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