

AF: Pathophysiology and Progression

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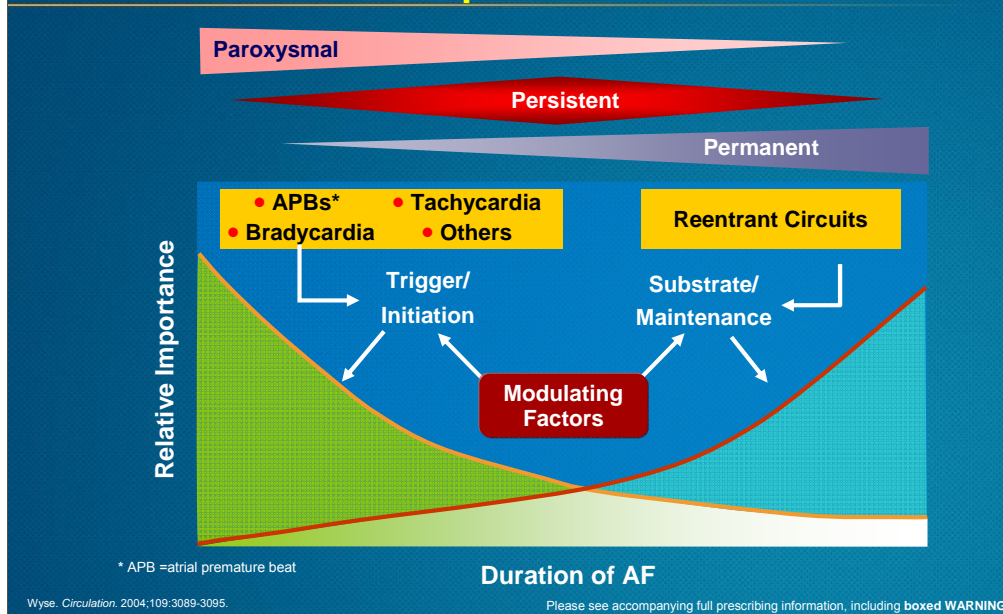
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DR. PRYSTOWSKY:

So to start off tonight, let me pass the program over to Dr. Grant, who is going to talk to the pathophysiology and progression. Gus?

AUGUSTUS GRANT, MD: Good evening. My first slide gives a clinical perspective on atrial fibrillation.

AF: The Clinical Perspective



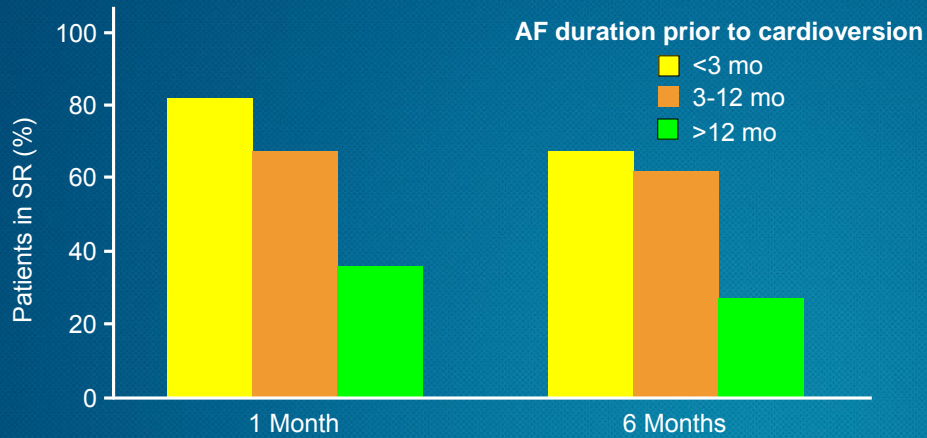
DR. GRANT:

Usually atrial fibrillation starts out in its paroxysmal form, consisting of brief self-terminating episodes of atrial fibrillation.

It may eventually progress to become persistent atrial fibrillation in which antiarrhythmic drugs, or a DC cardioversion is required to restore normal sinus rhythm. In the final analysis, it may progress to permanent atrial fibrillation in which sinus rhythm can no longer be maintained. The factors that are important in modulating atrial fibrillation varies along this clinical spectrum, such that, for example, with paroxysmal atrial fibrillation, atrial premature beats, bradycardia, and tachycardia are important initiating events. In its persistent form, we know that the autonomic nervous system is important in modulating atrial fibrillation.

We have come to recognize a vagal form of atrial fibrillation, which usually occurs at night, and is associated with slower rates, and sympathetic forms of atrial fibrillation that occur in patients who have other forms of heart disease. Persistent atrial fibrillation so modifies the properties of the atrium, and in particular the structural properties of the atrium, to set up the reentrant circuits that cause atrial fibrillation to become persistent.

Greater SR Maintenance is Achieved With Earlier Cardioversion



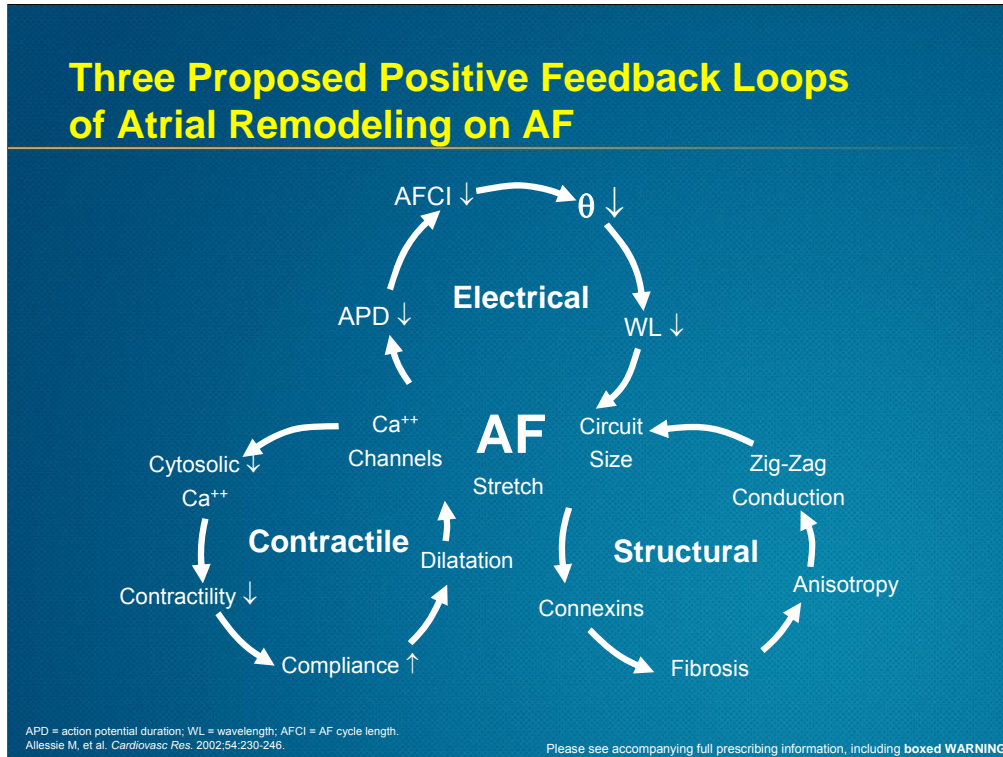
Dittrich HC, et al. *Am J Cardiol.* 1989;63:193-197.

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DR. GRANT:

These are clinical data looking at the relationship between the prior duration of atrial fibrillation and the maintenance of normal sinus rhythm following DC cardioversion. Patients are arranged in three groups, those who have atrial fibrillation for three months or less, those who have atrial fibrillation for 3 to 12 months, and those who have been atrial fibrillation for more than 12 months. As the slide shows, at both one month and six month period when the patients are evaluated, you're less likely to remain in normal sinus rhythm the longer you're in atrial fibrillation.

Three Proposed Positive Feedback Loops of Atrial Remodeling on AF



DR. GRANT:

Based on those data and other experiments, one can propose that electrical, contractile, and structural remodeling occurs in atrial fibrillation. And further, the data suggests that, in fact, the calcium channel is critical. The decline in the calcium channel current results in abbreviation of the action potential duration and effective refractory period, a decrease in the atrial fibrillation cycle length, a slowing of conduction, and a decrease in the wavelength. Now, we'll get back to this concept of wavelength later in the presentation, but it is a product of the effective refractory period, and the conduction velocity.

The decline in the calcium channel current also leads to a decrease in cytosolic calcium concentration, a decrease in contractility of the atrium, increase in its compliance, atrial dilatation, and stretch. The stretch initiates a series of factors that are important in the synthesis of structural proteins in the atrium, such as the connexins. It increases their currents of fibrosis, the fibrosis leads to anisotropy, which sets up the pathway for the slow conduction that's critical in permanent atrial fibrillation.

Mechanisms for AADs in Treatment of Cardiac Arrhythmias

- Targets (ectopic foci, reentrant circuits)¹
- Membrane electrogenic mechanisms
 - Voltage-gated ion channels (Na, Ca, K, Cl, etc) and subtypes²
 - Ligand-gated ion channels (ACh, ATP, etc)²
 - Electrogenic transporters (Na-K, Na-Ca)²
 - Gap junctions³
- Membrane and intracellular receptors/signaling²
- Substrate – renin-angiotensin activation inhibition, etc³

AADs = antiarrhythmic drugs.

1. Nattel S. *Nature*. 2002;415:219-226.
2. Nattel S, et al. *Circ Arrhythm Electrophysiol*. 2008;1:62-73.
3. Fuster V, et al. *Circulation*. 2006;114:e257-354.

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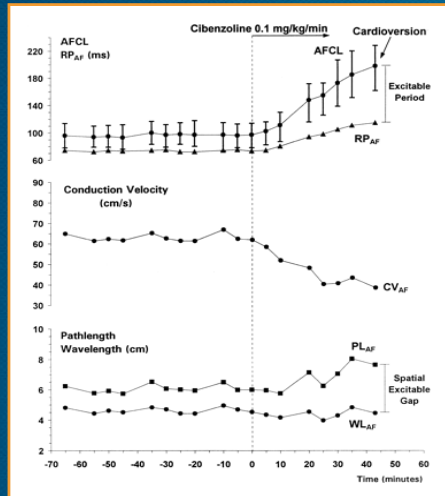
DR. GRANT:

Antiarrhythmic drugs are the targets for restoring normal sinus rhythm in atrial fibrillation. Now, how do these drugs act? We think critical targets for antiarrhythmic drugs action are the voltage-gated ion channels such as the sodium channel, a calcium channel, and the potassium channels, and their various subtypes. Certain ligand-gated ion channels are important, particularly the acetylcholine-activated channel. Potential targets include transporters like the sodium potassium-ATPase. Membrane and intercellular signaling receptors, and then certain substrates. There are data suggesting that inhibition of the renin angiotensin system might actually prevent atrial fibrillation recurrence. But for the remainder of the presentation we will focus on the drugs that act on membrane ion channels.

1. Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. *Circ Arrhythm Electrophysiol*. 2008;1:62-73.
2. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation*. 2006;114:e257-354.

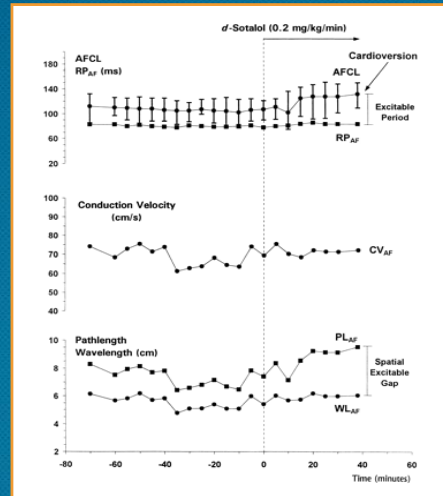
AAD Action in AF

Class I Drug Action



Wijffels MC, et al. *Circulation*. 2000;102:260-267.

Class III Drug Action



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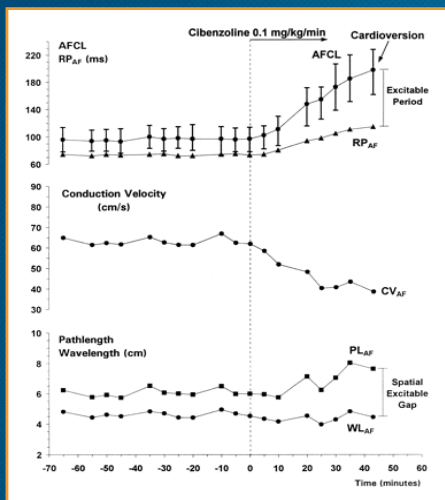
DR. GRANT:

This slide compares the action of class I antiarrhythmic drugs, which are the sodium channel-blocking drugs, and class III antiarrhythmic drugs with either potassium channel-blocking drugs on certain of the properties that one observes in atrial fibrillation and experimental model.

If one looks in the upper part of the panel on the left, the antiarrhythmic drug is administered on the vertical broken line. One can see that following drug administration, the atrial fibrillation cycle length prolongs. That is the atrial fibrillation slows. Immediately below that we see that the effective refractory period is also prolonged by the sodium channel blocker, though to a lesser extent. The result is that the excitable period, that interval between the atrial fibrillation cycle length and the wavelength is actually increased.

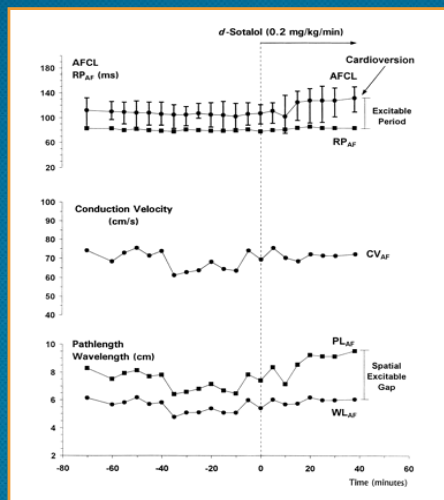
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DR. GRANT: (CONT'D)

The sodium channel-blocking drug slows conduction, with the result that, if one looks in the lower part of the panel, one can see that the wavelength of atrial fibrillation is actually unchanged. But at the time of atrial fibrillation termination, it is the interval between the atrial fibrillation cycle length, and the effective refractory period that is prolonged. That is the excitable gap.

If you look at the story with a class III drug shown on the right, one also sees that following initiation of drug administration, the atrial fibrillation cycle length also prolongs. However, the effective refractory period is not prolonged to the same extent. The result also is that the excitable gap is prolonged during drug administration, and is prolonged at the time of atrial fibrillation termination. Notice that the conduction velocity shown in the middle, and the wavelength shown on the bottom are unaltered. The message from these two experiments, then, is that prolongation of the excitable gap in atrial fibrillation appears to be critical to its termination, and this prolongation can occur either with a class I drug, or a class III drug.

Wijffels MC, Dorland R, Mast F, Allesie MA. Widening of the excitable gap during pharmacological cardioversion of atrial fibrillation in the goat: effects of cibenzoline, hydroquinidine, flecainide, and d-sotalol. *Circulation*. 2000;102:260-267.

Interpretation of Mechanism of Drug Action in AF

- The stability and persistence of AF is dependent on the number of circulating wavelets in the atria
- Wavelets have a relatively short lifetime
 - Δ in wavelet # = Formation – Extinction
- \uparrow in excitable period \rightarrow Fusion of existing wavelets; Fewer wavelets \rightarrow termination

Nattel S. *Nature*. 2002;415:219-226.

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DR. GRANT:

How do we interpret this prolongational excitable period as an antiarrhythmic mechanism? Well, we know that the stability and persistence of atrial fibrillation is dependent on a number of wavelets circulating in the atrium. Wavelets have a relatively short half-life, and the change in a number of wavelets is the difference between the number that are being formed, and the number that undergo extinction. And increase in the excitable period results in fusion of existing wavelets. Fewer wavelets are then present in the atrium, and this leads to atrial fibrillation termination.

Mechanism of Multichannel Blockers

- I_{Kr} , I_{Ks} , & I_{KACH} block with little reverse use dependence
 - APD, ERP ↑↑
- I_{Na} block
 - Inactivated state block → ↑↑ Block as the APD ↑
- I_{Ca} block
 - ↓ Sinus node
 - ↓ AV conduction velocity ↓ in the ventricular response in AF

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DR. GRANT:

The multi-ion channel blockers, such as amiodarone and dronedarone, interact with most of these critical channels that control the action potential. They block the rapid component of the delayed rectifier, the slow component, the acetylcholine activated current, and they block these channels with little so-called reverse use dependence. That is the extent of block does not depend in a critical way on the rate of stimulation. This is, in fact, opposite the case with other drugs like quinidine. These drugs also block the sodium channel, and they block the sodium channel when it's in its inactivated state. The action potential prolonging effect that results from the potassium channel blockade, potentiates this inactivation state block of the sodium current. Lastly, the multi-channel blockers block the calcium current. Therefore, they slow conduction in regions of the heart where the calcium current is critical. For example, in the sinus node, and in the AV node where they can, in fact, decrease the ventricular response in atrial fibrillation.

Summary

- Multiple mechanisms contribute to the occurrence of AF
 - Reentry
 - Rapid focal discharge with fibrillatory conduction
- Rapid atrial rates result in electrical, mechanical and structural remodeling; the changes all favor the persistence of AF
- Drugs remain the mainstay of treatment of AF
- Multi-ion channel blockers offer the most favorable effect with less TdP

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DR. GRANT:

To summarize then, multiple mechanisms contribute to the occurrence of atrial fibrillation. This includes reentry, and a rapid focal discharge with fibrillatory conduction. Rapid atrial rates result in electrical, mechanical, and structural remodeling of the atrium, changes that favor the persistence of atrial fibrillation. At the present time drugs remain the mainstay of treatment of atrial fibrillation. The multi-ion channel blockers such as amiodarone and dronedarone offer the best opportunity for restoring and maintaining normal sinus rhythm in atrial fibrillation.

ERIC PRYSTOWSKY, MD, FACC: So Gus, let me ask you something. You mentioned earlier that there was this schema of paroxysmal persistent and permanent. That gives one the feeling that there is inevitability in this continuum. Are there data to suggest that may not be true? I mean that not every person is bound to have permanent AFib?

1. Blaauw Y, Schotten U, van Hunnik A, et al. Cardioversion of persistent atrial fibrillation by a combination of atrial specific and non-specific class III drugs in the goat. *Cardiovasc Res.* 2007;75:89-98.
2. Nattel S, Burstein B, Dobrev D. Atrial remodeling and atrial fibrillation: mechanisms and implications. *Circ Arrhythm Electrophysiol.* 2008;1:62-73.

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DR. GRANT: (CONT'D)

AUGUSTUS GRANT, MD: Absolutely. There are data indicating, and these data are, in fact, obtained from a large core study done in Olmsted County in Minnesota, where they show that the progression that I showed on that slide about the clinical perspective of atrial fibrillation is not inevitable. About a third of patients that present with paroxysmal atrial fibrillation will run true to form, and that's the only form of atrial fibrillation that they'll have throughout the course of their illness. Another proportion of patients will have persistent atrial fibrillation, but we can maintain normal sinus rhythm in them most of the time by use of an antiarrhythmic drug. And then there is a group, perhaps 20 or 30 percent of patients, who will go into permanent atrial fibrillation with or without drug use.

ERIC PRYSTOWSKY, MD, FACC: Thanks, Gus.

1. Blaauw Y, Schotten U, van Hünnik A, et al. Cardioversion of persistent atrial fibrillation by a combination of atrial specific and non-specific class III drugs in the goat. *Cardiovasc Res.* 2007;75:89-98.
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