Today, I'd like to talk to you about…

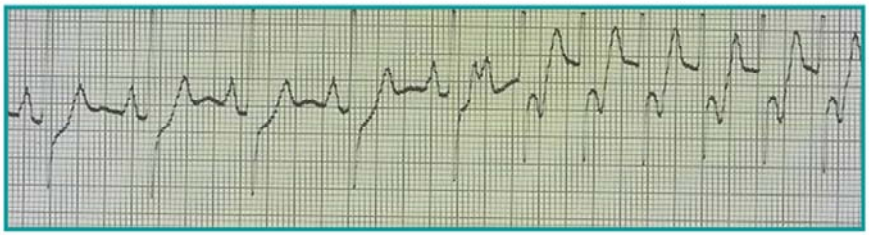
Terminology and Diagnosis

Atrial Fibrillation

- Atrial Fibrillation vs. Atrial Tachycardia
  - Atrial Tachycardia
    - Atrial rate 160 to 240 bpm
    - Atrial rhythm is essentially regular
    - Ventricular rate can be regular or irregular depending on status of AV nodal conduction
    - Site of origin is an ectopic foci in the atrium other than the SA node or reentry
    - Usually only a single P wave for each QRS

Atrial Fibrillation

- Atrial Tachycardia (AV Nodal Reentry)



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Atrial Fibrillation

- Atrial Fibrillation vs. Atrial Flutter
  - Atrial Flutter
    - Atrial rate 240 to 350 bpm
    - Atrial rhythm is regular
    - Ventricular rhythm is regular if AV conduction ratio is constant
    - Macro-reentrant pathway involving the entire right atrium
    - Typically has a saw-tooth pattern on ECG

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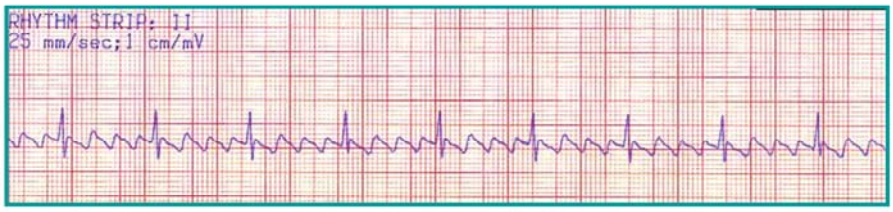
Atrial Fibrillation

- Atrial Flutter



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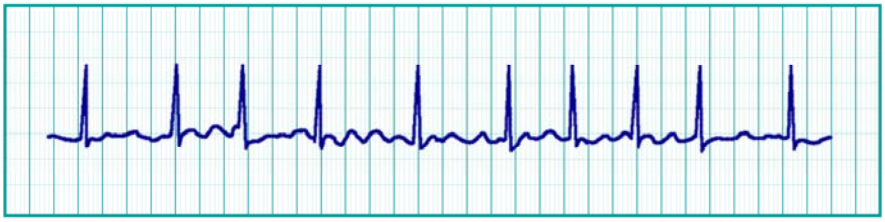
Atrial Fibrillation

What is Atrial Fibrillation?

- Chaotic circular impulses in the atria
  - Several reentrant circuits moving simultaneously
  - Atrial rates
    - 300 to 600 beats per minute
  - Ventricular rates regulated by the AV node
    - Irregularly irregular due to partial depolarization of AV node
  - Results in loss of AV synchrony
    - 20% to 30% decrease in cardiac output

Atrial Fibrillation



Cardiac output is compromised by

- Loss of atrial transport
- Short cycles preclude adequate ventricular filling

Rapid Rates predispose to Ventricular Dysfunction

Stasis predisposes to clots and systemic emboli

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Incidence and Prevalence

Incidence and Prevalence

- Atrial fibrillation is one of the most common arrhythmias
- Over 5 million people worldwide are affected by this disease
- Over 2 million in the US alone

Incidence and Prevalence

- Prevalence increases with age
  - 4.8 % in the 70-79 age group
- Increases to
  - 8.8% in the 80-89 age group
- During the next 7-8 years, the number of people over the age of 80 is expected to quadruple

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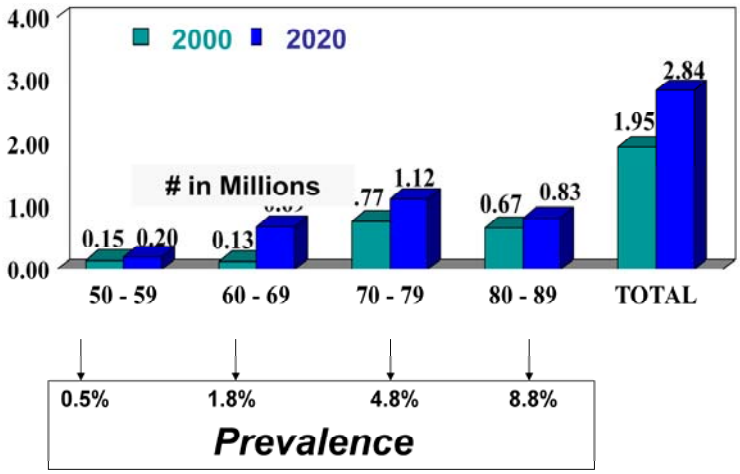
Atrial Fibrillation: U.S. Experience



Furberg, Am J Cardiol 1994; 74: 236 - 41.

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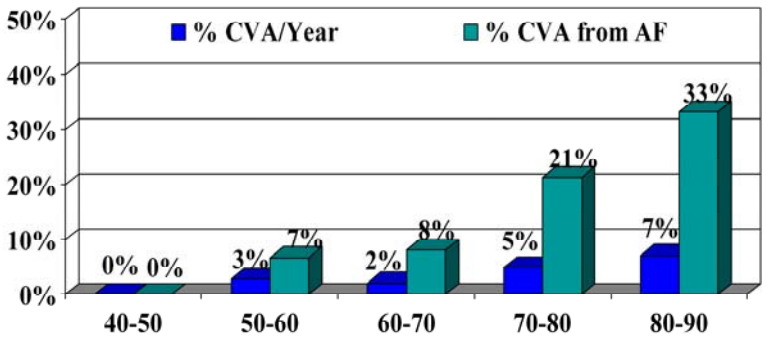
Atrial Fibrillation - Age & CVA



Adapted from Fuster V et al. 1997.

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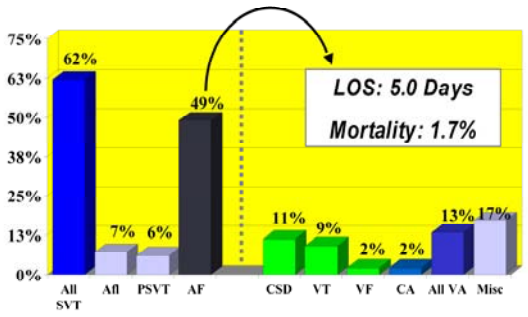
Atrial Fibrillation

- AF accounts for about half of all hospital days related to arrhythmia diagnosis

Arrhythmia Discharge Diagnoses



Adapted from HCIA, Inc. Database, 1997

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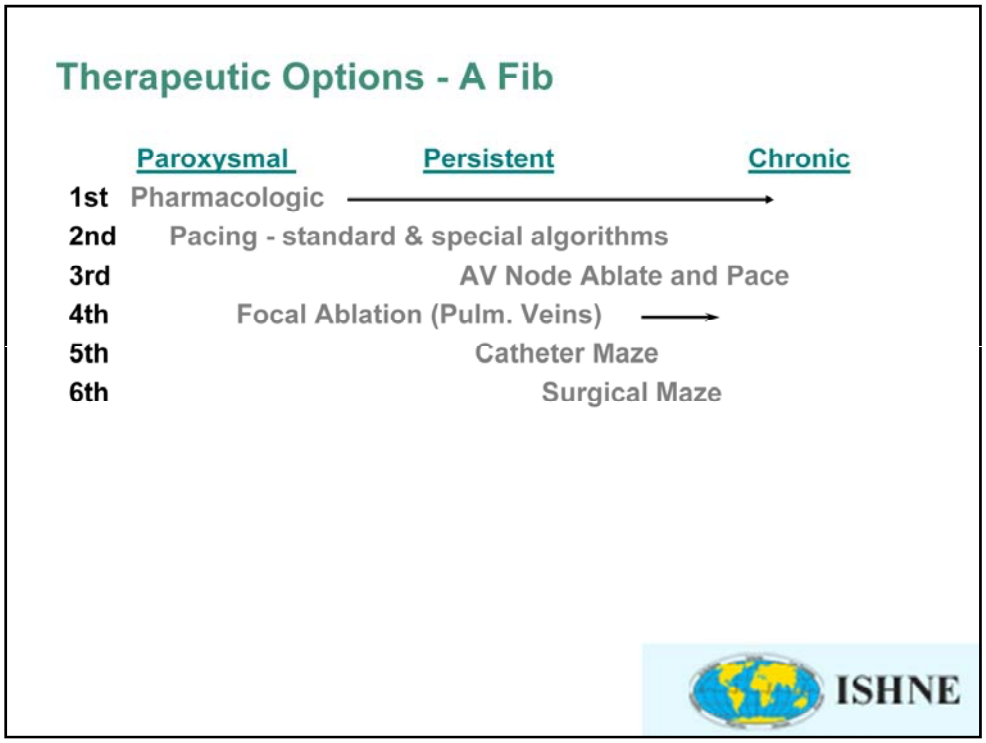

Therapeutic options for Atrial Fibrillation

Given the multiplicity of causes for atrial fibrillation as well as the varied manifestations, it is unlikely that a single therapy will work for all patients. In addition, the final therapeutic regimen is likely to be a hybrid combining both drugs as well as devices or other invasive procedures. Further, given the progression of disease over time, a therapy that is effective at the beginning may no longer be effective as the disease evolves.

First line of therapy is and will continue to be pharmacologic. In the absence of underlying coronary artery disease, the Class I-C agents (propafenone, flecainide) appear to be very effective. In the presence of CAD, the class III agents such as sotalol and amiodarone. There are new agents presently under investigation. Digitalis, beta blocker and calcium channel blockers are primarily used to control the ventricular response to AF.

In the setting of a bradycardia (sinus node dysfunction), atrial-based pacing has proven to be effective in reducing the incidence of chronic atrial fibrillation. Various algorithms such as DAO are presently under study but the results are optimistic.

We are learning that paroxysmal atrial fibrillation may start from a very localized focus, one common area being the right or left superior pulmonary veins. Focal ablation or focal linear ablation scars may delay if not cure AF. Finally, atrial defibrillation or the surgical MAZE procedure.

Symptoms and Diagnosis

Symptoms

- Heart palpitation
  - A sudden pounding, fluttering or racing feeling in the chest
  - **90% of AF episodes may be asymptomatic!**
- Lack of energy or feeling overtired
- Dizziness
  - Lightheaded or faint
- Shortness of breath
- Chest discomfort
- Patients with other heart disease may feel worse

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Diagnosis

- Patient symptoms
- ECG
- Holter monitor
- Event monitor
- Transtelephonic monitor

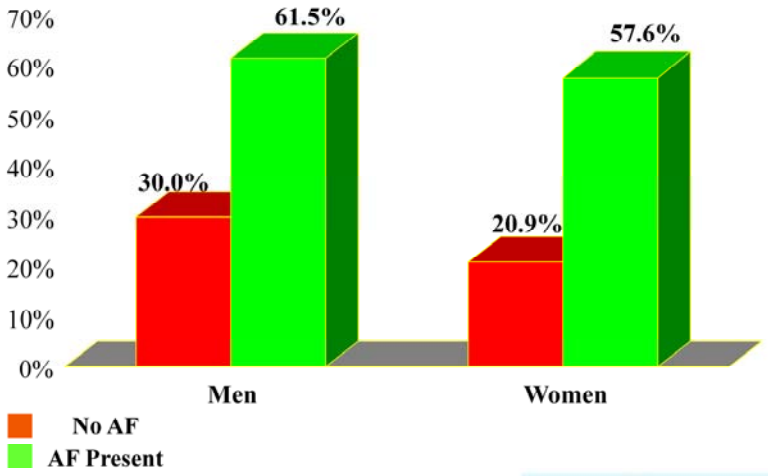
Associated Risks

Risks Associated with Atrial Fibrillation

- Death
  - Men with AF have a 1.5 times greater risk of death than men without AF
  - Women with AF have a 1.9 times greater risk of death than women without AF

Risks of Atrial Fibrillation

- Long-term Mortality Rates Framingham Study



Benjamin EJ et al. Circ 1998; 98: 946-52.

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Risks of Atrial Fibrillation

- Paroxysmal & Chronic Atrial Fibrillation - Risk of Thromboembolism

Study	CVA Rate (% /Year)	
	Paroxysmal	Chronic
BAATAF	2.5%	2.8 %
SPAF	5.6%	5.9 %
Peterson et al.	2.0%	5.1 %
Roy et al.	5.3%	5.4 %
Fortin et al.	2.0%	-

Risks of Atrial Fibrillation

- Stroke
  - Patients with AF are 5 times more likely to have a stroke than the general population
- Cause of 75,000 cases of stroke annually
- 23% of all strokes in the U.S.

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Risks of Atrial Fibrillation

- Heart Failure
  - Result of fast ventricular rates
    - Decreased cardiac output
    - Ventricular tachyarrhythmia myopathy
- An estimated 25% of heart failure patients also have atrial fibrillation
- AF may be caused by heart failure or it may be the cause of heart failure

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Causes

Most Common Associations

- Hypertension
- Coronary artery disease
- Post heart surgery
- Chronic lung disease
- Heart failure
- Cardiomyopathy
- Congenital heart disease
- Pulmonary embolism

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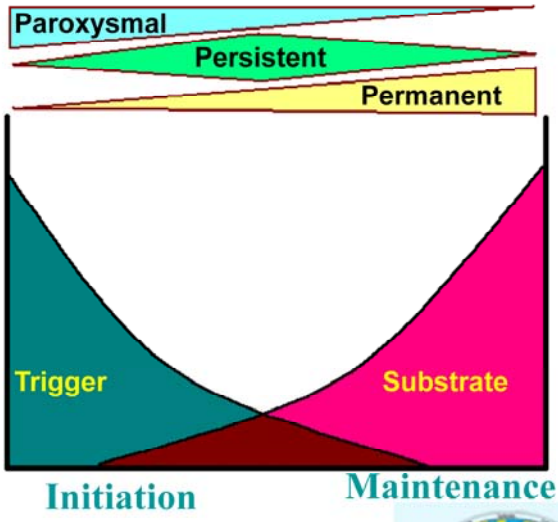
Stages

Stages of Atrial Fibrillation

- Paroxysmal
- Persistent
  - New persistent
  - Long persistent
- Permanent

Relative Importance

Triggers vs Substrate



Adapted from D. Packer 1/2000

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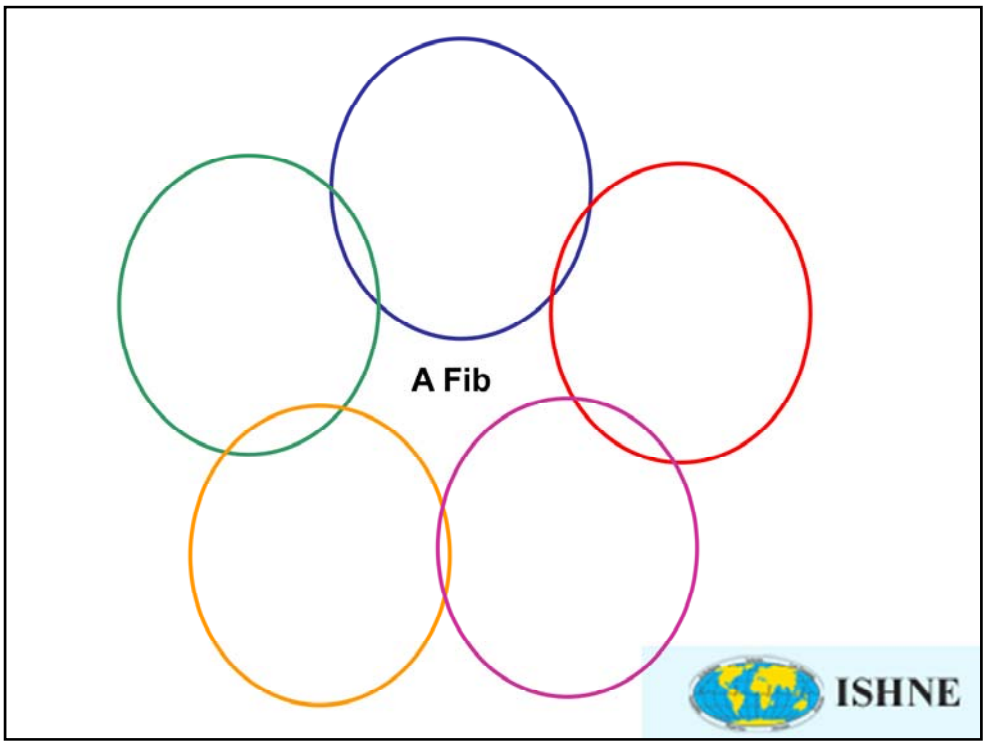


Based on the 14th Boston AF Symposium held in January 2009, the overview of atrial fibrillation has markedly increased in complexity. At the same time, there are many more options to try to prevent the problem or treat the rhythm once it has started to occur.

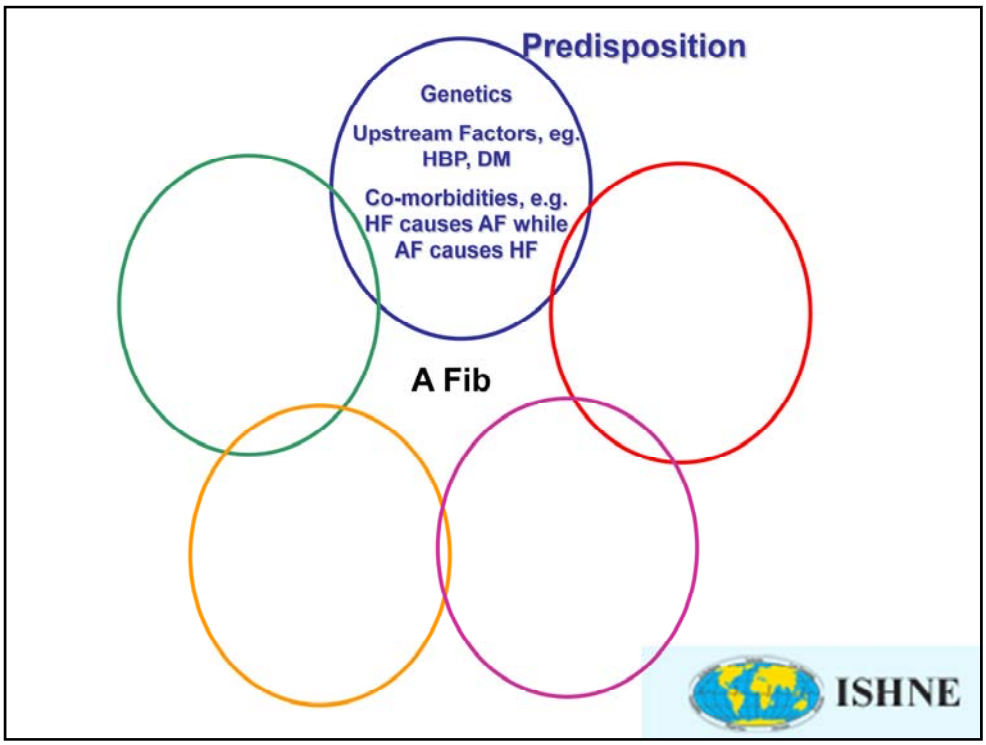
Therapeutic targets – statins may be effective in modulating/reducing fibrosis. There is gap junction modulation and newer antiarrhythmic drugs. The best of the ones on the horizon to be approved is dronedarone (an analog of amiodarone). There are other atrial or even left atrial sodium blockers that are looking very good in the basic science lab.

5. Ablation is proving increasingly effective but we need to identify the appropriate target. Paroxysmal AF is easier to treat than persistent AF. The techniques with improved catheters and introducers are being developed along with EP guidance as well as Image Guidance and Robotics to provide finer control

Factors predisposing to AF include genetics (Lone AF in the young patient is believed to be a genetic abnormality although all the genetic sites have not been identified), upstream factors – factors like hypertension and diabetes that will predispose to wall stress and increased atrial fibrosis. There are also co-morbidities that place a stress on the atrium such as heart failure.

The myocardial substrate may be directly affected by remodeling on the cellular level. Sustained fast rates results in a decrease in calcium ingress which decreases contractility. It also predisposes to increased atrial fibrosis which increases the likelihood of AF. Maurits Allessie “AF begets AF” – the longer the patient is in AF, the more likely it is that the patient will stay in AF. There are electrogram factors. If AF can be terminated, even with repeated cardioversions there is a reverse remodeling favoring the maintenance of sinus rhythm (Sinus rhythm begets sinus rhythm)

Anatomy – there is the atrial electrical anatomy, triggers arising from one or more of the pulmonary veins, variations in autonomic (sympathetic and parasympathetic innervation) and non-venous areas of interest in the atrium. It is not only the pulmnary veins.



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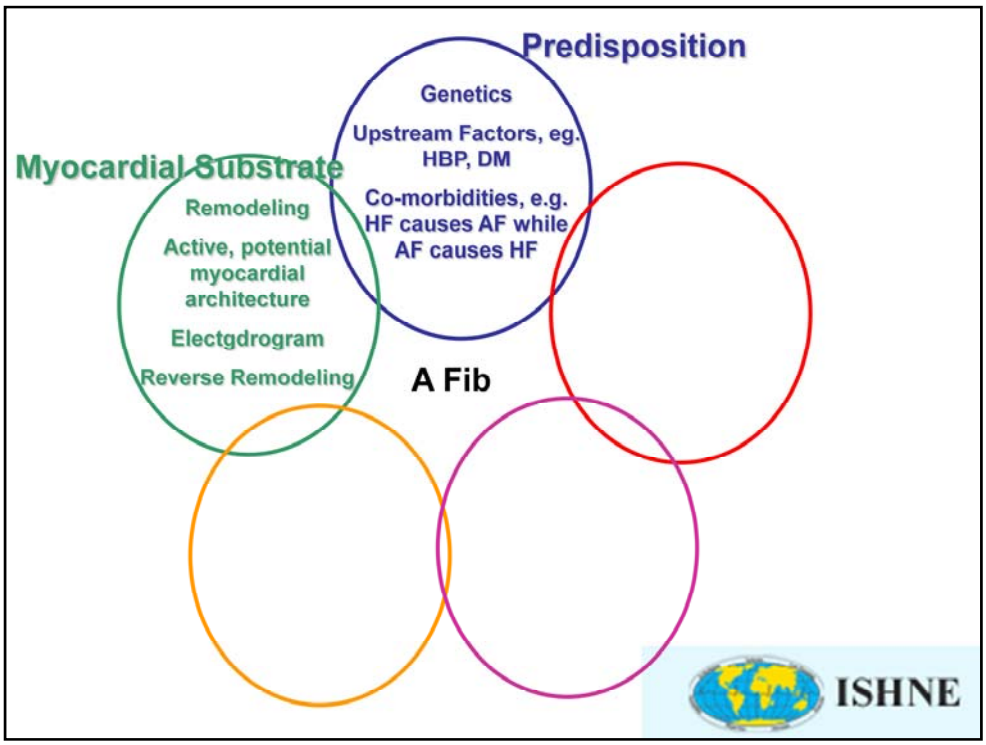

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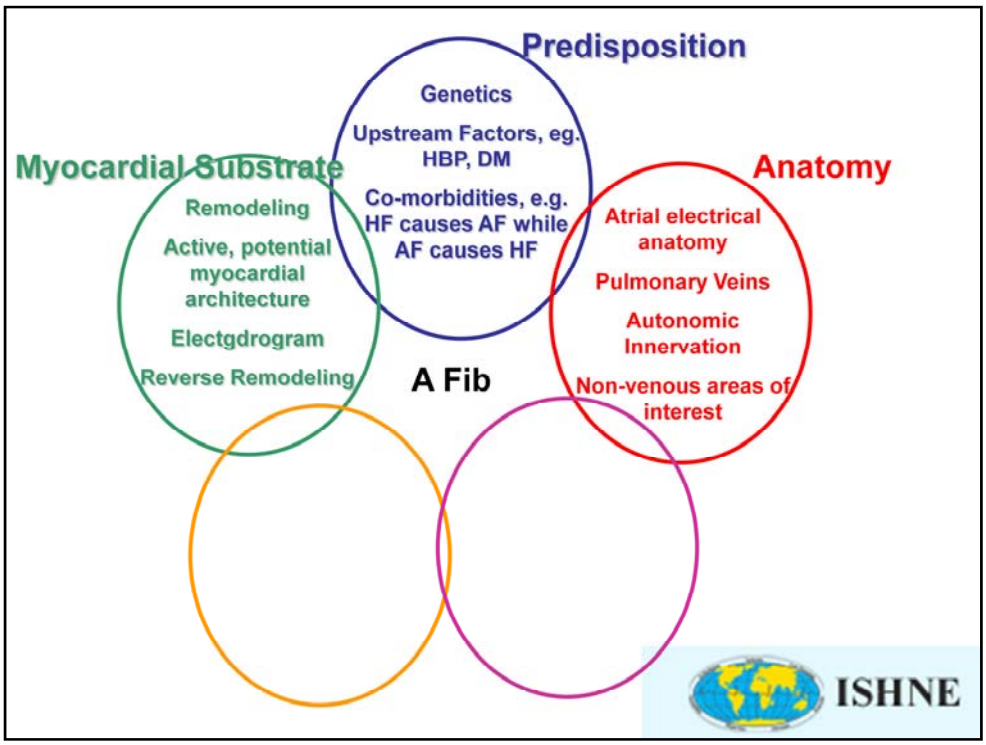

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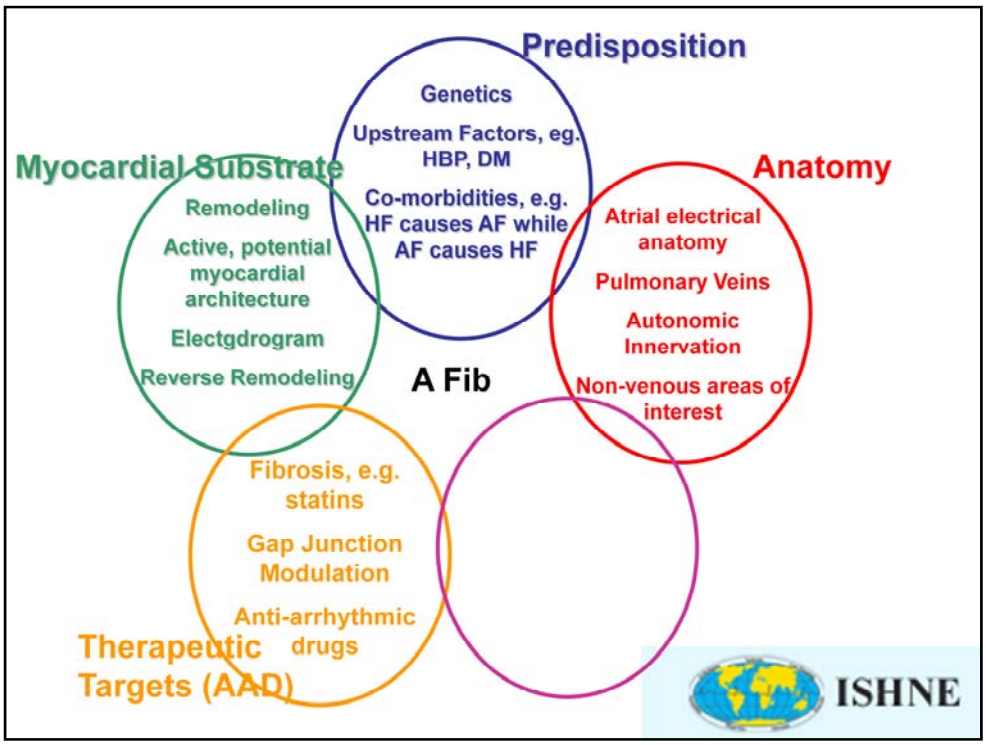

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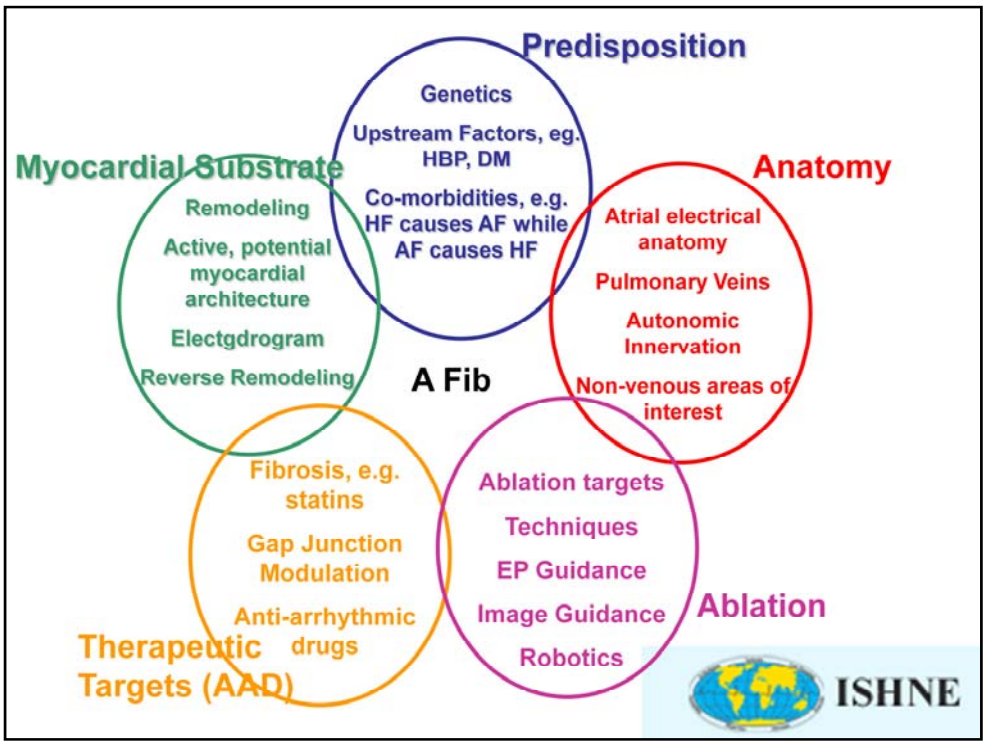

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Stages of Atrial Fibrillation

- Paroxysmal (23% of AF population)
  - Self limiting
    - Spontaneous conversion to sinus rhythm within 24 hrs after onset is common
    - Once the duration exceeds 24 hrs, the likelihood of conversion decreases
    - After one week of persistent arrhythmia, **spontaneous conversion is rare**
  - 30% of these patients develop "Persistent" AF

Stages of Atrial Fibrillation

- Persistent (38% of AF population)
  - Requires intervention to restore normal rhythm
    - Cardioversion
      - Electrical or Chemical (drugs)
  - Can lead to electrical and structural changes in the myocardium (remodeling) that can lead to "Permanent" AF
  - AF duration of greater than 7 days rarely spontaneously converts
  - Since can now convert (via ablation) "permanent AF", some are calling this "long persistent AF"

Stages of Atrial Fibrillation

- Permanent (39% of AF population)
  - Unable to convert

  However
  - Pulmonary vein isolation and catheter Maze procedures may restore organized atrial rhythm
  - Ablation of parasympathetic ganglia behind the left atrium may restore sinus rhythm

Stages of Atrial Fibrillation

- Remodeling
  - Mechanical
    - Gradual atrial stretching leading to atrial enlargement caused by atrial fibrillation of long duration
    - Progressive atrial enlargement produces further degenerative changes favoring formation of reentrant circuits
    - Protracted periods of AF result in local hormonal changes that increase atrial fibrosis
    - Gap junction abnormalities
  - AF begets AF! (M. Allessie)
    - Associated with electrical remodeling
    - Persistent rapid atrial rates increases fibrosis

Stages of Atrial Fibrillation

- Remodeling
  - Electrical
    - Altered cellular electrophysiology in the atrial tissue
    - Shortening of atrial refractory period
    - Loss of normal lengthening of atrial refractoriness at slower heart rates
    - Increased atrial fibrosis

- **Sinus rhythm begets sinus rhythm**
  - Initial studies by InControl
  - Effectively reverse remodeling

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Atrial Fibrillation

- Summary
  - Very prevalent disease that will increase as the number of individuals with the graying of the population
  - Decreased quality of life for the patient
  - Significant associated morbidity (death, stroke and heart failure)

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Treatment of Atrial Fibrillation

Treatment of Atrial Fibrillation

- 30% of all AF patients are not diagnosed
- 70% of AF patients are suitable for treatment of which:
  - 30-50% drug treatment is effective
  - 50% do not respond to drugs and are suitable for RF ablation, surgical Maze procedure, or other treatments
  - New drugs (Dronedarone – 2009) and selective sodium channel blockers may increase the effectiveness of pharmacologic Rx
- Those who respond to drugs initially may develop resistance or breakthrough at a later date

Treatment of Atrial Fibrillation

- Categories of treatment
  - Rhythm
    - Regaining and maintaining normal heart rhythm
    - Prevention of HF and systemic embolism
  - Rate
    - Control of ventricular heart rate
    - Prevent symptoms, HF and dysfunction
  - Prevention of clotting and stroke

Treatment of Atrial Fibrillation

- Rhythm Control
  - Drugs
  - Cardioversion
  - Devices
  - Ablation
  - Surgery

Treatment of Atrial Fibrillation

- Drugs
  - Conversion of AF to sinus rhythm
    - Class 1A (decrease conduction velocity, increase refractory periods of cardiac tissue, suppress automaticity)
      - Quinidine, Procainamide
    - Class 1C
      - Flecainide, Propafenone
    - Class III (decrease conduction velocity, increase refractory periods of cardiac tissue, suppress automaticity)
      - Amiodarone (Corderone, Pacerone)
      - Sotalol (Betapace)
      - Ibutilide (Corvert)
      - Dofetilide (Tikosyn)
      - Dronedarone (not FDA approved as of 2009)

Selective atrial sodium channel blockers investigational in basic science lab

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Treatment of Atrial Fibrillation

- Drugs
  - Maintenance of normal rhythm
    - Class 1A
    - Class III
    - Class 1C (decrease conduction velocity)
      - Flecainide
      - Propafenone
  - Drug choice depends upon patient's underlying heart disease
  - New investigational drugs impacting the ion-channels and selective for the atrium rather the ventricle are under study and look promising

Treatment of Atrial Fibrillation

- Potentially lethal side effects of antiarrhythmic drugs
  - Proarrhythmic effects
    - QT prolongation leading to Torsade de Pointes (Quinidine syncope)
    - Monomorphic VT (Flecainide)
  - Renal and hepatic impairment
  - Pulmonary complications (Amiodarone)
  - Autoimmune disease (Pronestyl)

Treatment of Atrial Fibrillation

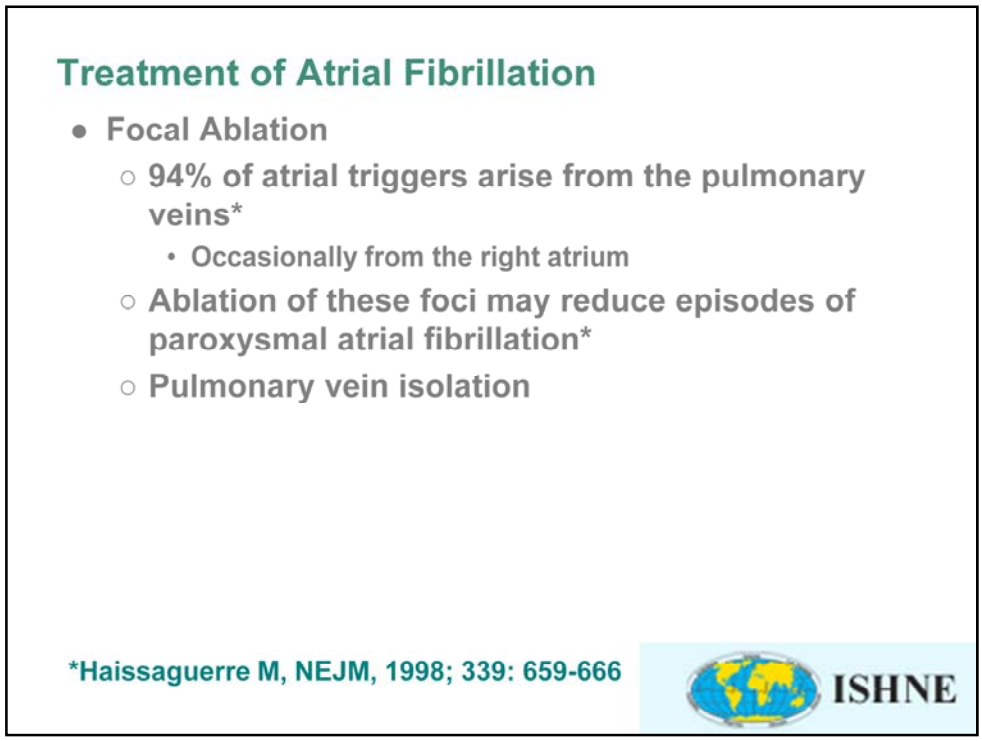
- Cardioversion
  - Electrical
    - Internal
    - External
  - Chemical (drugs)
    - Ibutilide (Corvert)
    - Dofetilide (Tikosyn)

Treatment of Atrial Fibrillation

- Associated with sinus node dysfunction (Brady-Tachy Syndrome)
  - Atrial pacing
    - Concomitant ventricular pacing may increase the propensity for AF
    - Ventricular pacing (DDD) in the setting of intact AV conduction can only occur with too short an AV delay which may raise intra-atrial pressure
  - Basic overdrive
    - Increased base rate
    - Rate modulation
  - Dynamic overdrive algorithms

Treatment of Atrial Fibrillation

- Devices
  - AF Suppression™ algorithm
    - St. Jude Medical (prevention)
  - AF termination with or without atrial ATP
    - InControl (no longer available)
      - Termination but not prevention
    - Medtronic (prevention and tachycardia termination)
      - AT500™ Pacing System
      - EnRhythm™

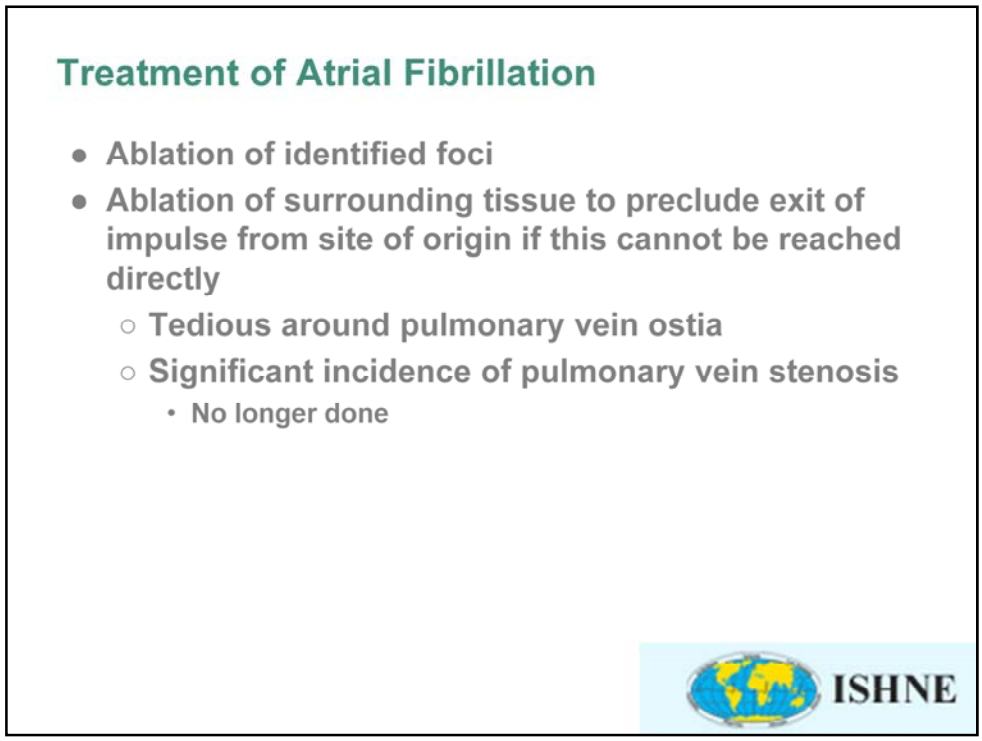


Focal Ablation for Paroxysmal Atrial Fibrillation

In patients with paroxysmal atrial fibrillation, the initiating trigger often arises in very localized areas. Recently, it has been demonstrated by a number of investigators that a predominance of these foci are within the superior pulmonary veins. Isolated foci have been demonstrated elsewhere in the atria. It is believed that if these foci can be eliminated as with ablation, the frequency of paroxysmal atrial fibrillation will be reduced and development of chronic atrial fibrillation delayed.

In this detailed study by Haissaguerre from France, the majority of these foci were deep within the pulmonary veins. On histologic examination, atrial myocardial fibers extend into the pulmonary veins lining the inside wall just within the endothelial layer.

However, reaching these areas is difficult requiring a puncture of the interatrial septum to reach the left atrium. Then, trying to manipulate an ablation catheter around and within one or more of the pulmonary veins further complicates the procedure.

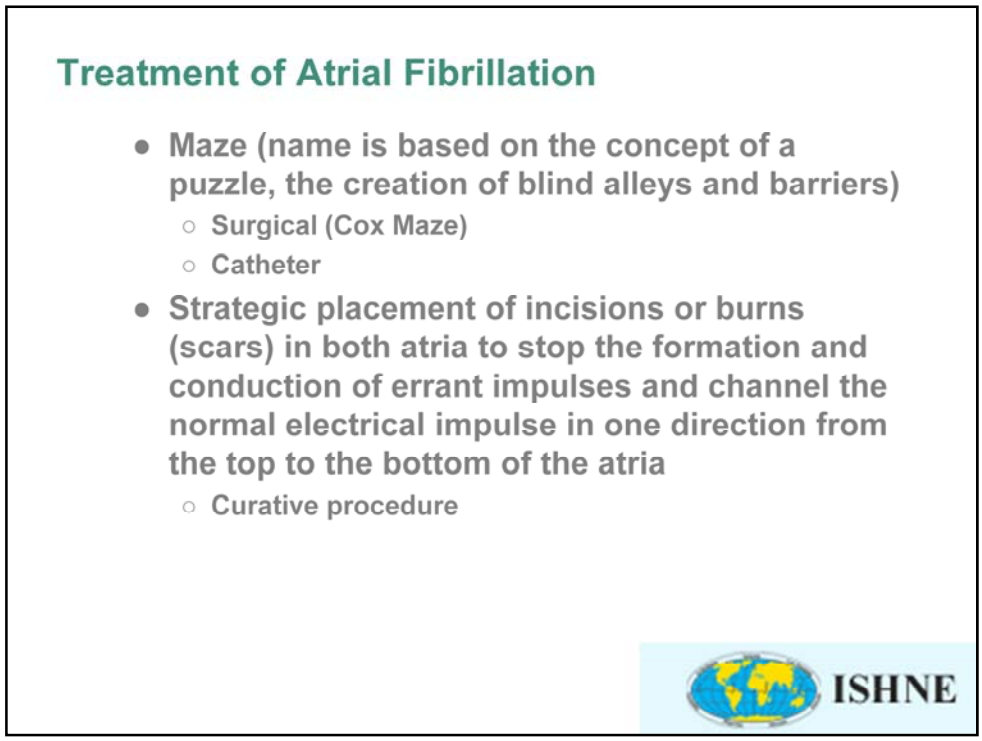


Focal Ablation

If there is an identified focus that starts the atrial fibrillation, ablation of that focus may offer some protective benefits. The other approach, if the specific focus cannot be reached, is to ablate around it precluding exit of the electrical impulse from that area hence preventing it from activating the rest of the atria.

With respect to the early studies involving the pulmonary vein ablation, creating a circumferential lesion around the pulmonary vein ostia is tedious. In addition, fibrosis forms in response to any injury and this may result in a progressive narrowing of the pulmonary vein where it enters the left atrium. This narrowing will obstruct the return of blood causing pulmonary congestion, pulmonary hypertension and shortness of breath with progressive exercise limitation. Obstruction of the pulmonary veins is called pulmonary stenosis.

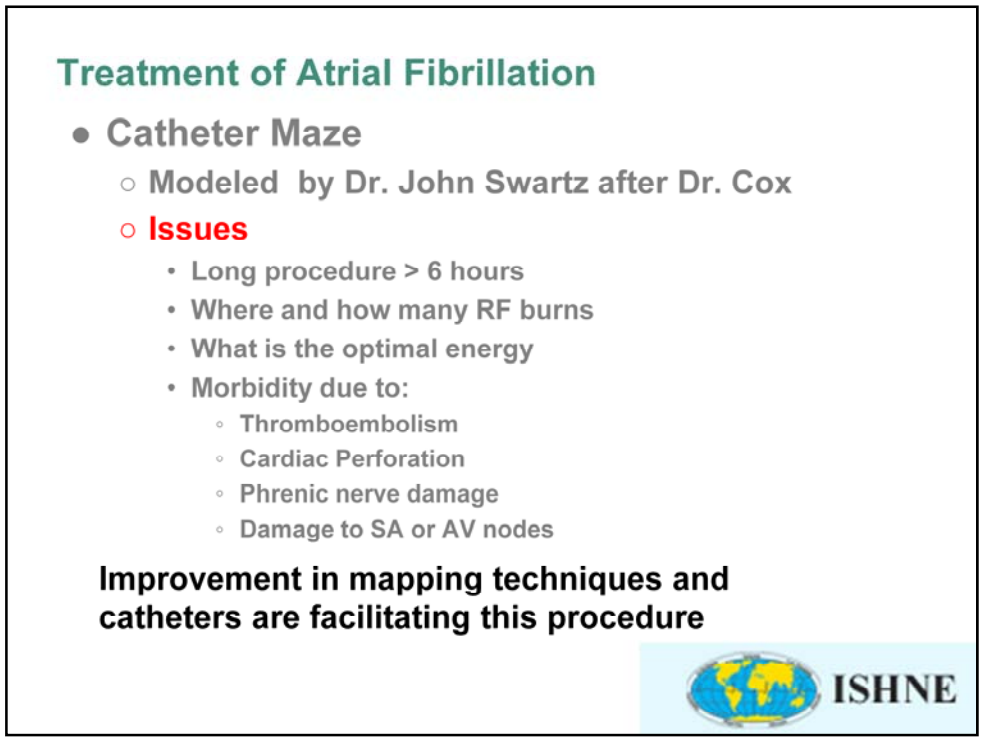
Before ablation of this area becomes a routine procedure, techniques to reach the pulmonary vein need to be improved. Also, a mechanism needs to be developed for “easy” ablation with minimal chance of late complications such as pulmonary stenosis. When these things happen, this may become a standard rather than an investigational procedure.



Lines of scar tissue are formed in the atria, either from a surgical incision, or as a result of RF energy application. The lines isolate areas of fibrillation, and then direct it along the path of the maze, resulting in a more coordinated contraction of the atria.

Treatment of Atrial Fibrillation

- Surgical Maze (Cox-Maze)
  - Introduced by Dr. James L. Cox in 1987
  - Issues
    - Usually median sternotomy
    - Bypass is required
    - Procedure time approximately 4 hours
    - Number and placement of incisions
    - Usual risks associated with bypass surgery



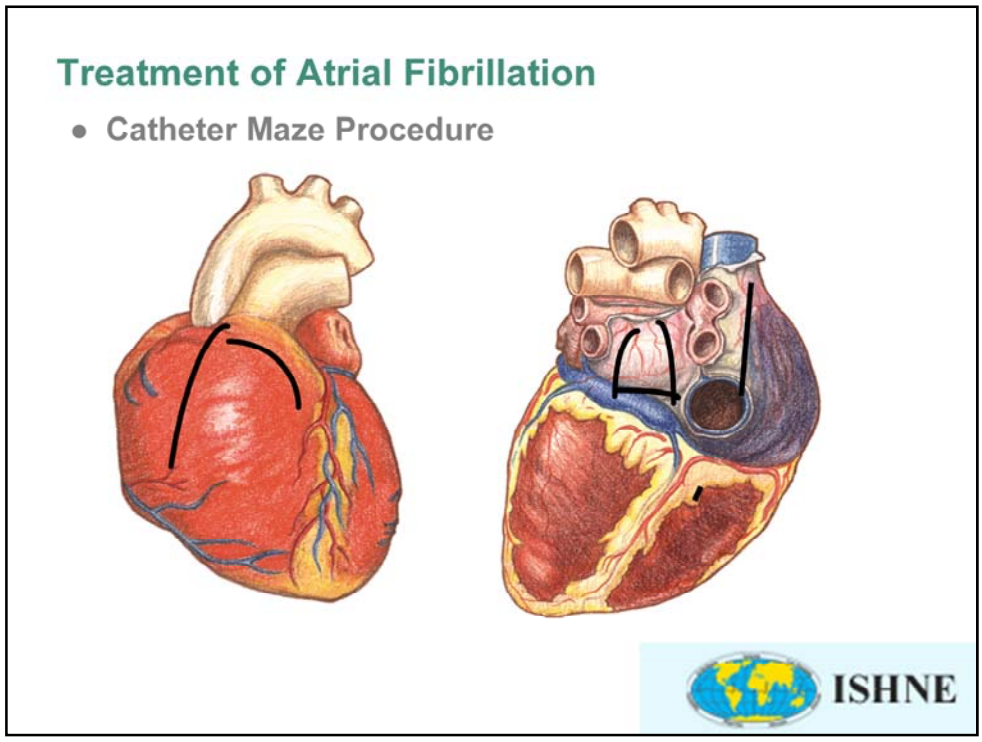
Catheter MAZE Procedure

Dr. John Swartz, a consultant to Daig, modeled a catheter procedure after the surgical MAZE procedure originally developed by Dr. James Cox. The idea is to compartmentalize the atrium reducing the critical mass in any area such that fibrillation cannot be maintained. The idea of this procedure is using ablation catheters using a drag technique, create a series of linear lesions along the lines diagrammed on these heart diagrams.

The first procedures demonstrated the feasibility of the technique but extended between 14 to 18 hours in the EP lab. It became so tedious that it was impractical. However, the feasibility was confirmed.

Now efforts are underway to improve the ablation catheters to shorten the length of the procedure.

The MAZE procedure has been relatively effective in restoring an organized electrical atrial rhythm but there may be a delay of weeks to months before there is a return of mechanical function and in some cases, the atrium does not provide an effective contraction.



Graphic showing some potential lines of scar formation in the atria caused by catheter application of RF energy.

Treatment of Atrial Fibrillation

- Summary of methods to regain and maintain normal heart rhythm
  - Drugs
  - Cardioversion
  - Devices (pacemakers)
  - Ablation
  - Surgery

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Treatment of Atrial Fibrillation

- Categories of treatment
  - Rhythm
    - Regaining and maintaining normal heart rhythm
    - Prevention of HF and embolism
  - Rate
    - Control of ventricular heart rate
    - Prevent symptoms, HF and dysfunction
  - Prevention of clotting and stroke
    - Oral anticoagulation
    - Left atrial appendage occlusion devices

Treatment of Atrial Fibrillation

- Control of Ventricular heart rate
  - Permanent AF
    - Patient symptoms are reduced with ventricular rate control
    - Patients are only aware of ventricular beats, not atrial
    - Uncontrolled rate can lead to ventricular dysfunction
      - CHF
      - Myopathy
    - Drug therapy appears to reasonably control ventricular rate at rest, but is not as effective during exercise.

Treatment of Atrial Fibrillation

- Heart Rate Control
  - Drugs
    - Beta Blockers
    - Calcium Channel Blockers
    - Digoxin
  - Ablation
    - AV nodal modification
    - AV nodal ablation with pacemaker implantation
      - PAVE Study – intentional use of biventricular pacing

Treatment of Atrial Fibrillation

- Drugs
  - Beta Blockers (decrease automaticity, increase refractory period, blocks endogenous catecholamines which facilitate increased AV nodal conduction and higher rates)
    - Metoprolol
    - Propanolol
    - Atenolol
    - Esmolol (acute testing, transient effect)

Treatment of Atrial Fibrillation

- Drugs
  - Calcium Channel Blockers (increase refractory period of AV node thus controlling ventricular response)
    - Diltiazen
    - Verapamil
  - Digoxin (increase refractory period of AV node by acting in CNS to increase vagal tone thus controlling ventricular response)
    - Shortens atrial myocardial refractory period which may facilitate persistent or development of AFib

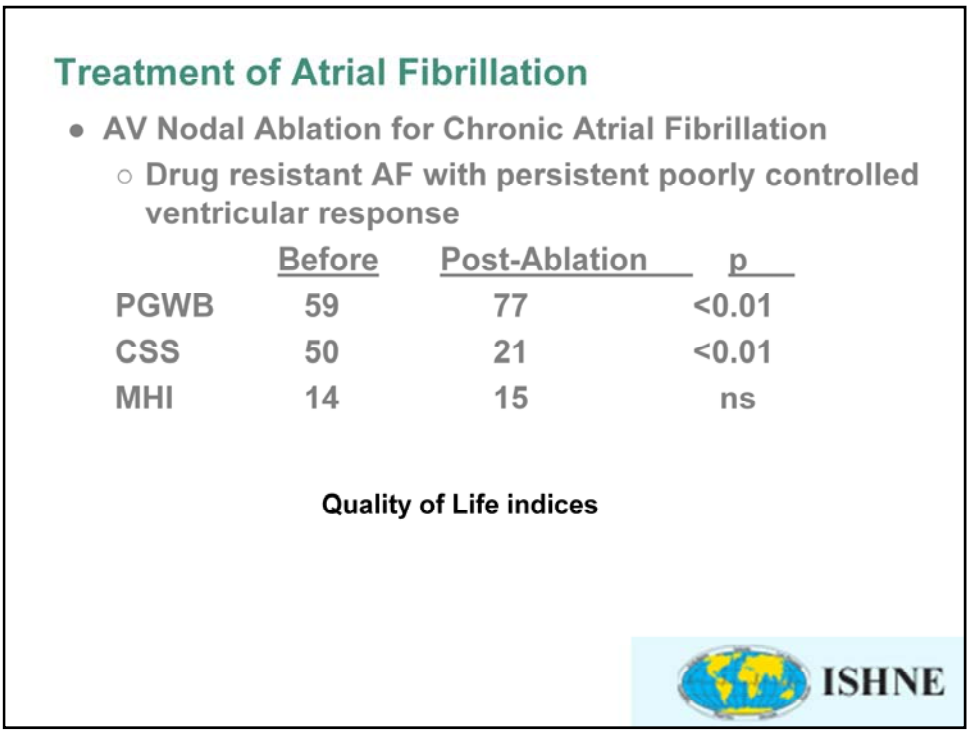
Treatment of Atrial Fibrillation

- Ablation
  - AV nodal modification
    - Infrequently used
    - Modification of AV nodal tissue to slow ventricular rate using catheter ablation techniques
    - Most attempted modifications become ablations
  - AV nodal ablation "Ablate and Pace"
    - Total interruption of AV conduction
    - Requires permanent pacemaker implantation
    - Should try to do as high as possible to allow for a junctional escape focus should a problem develop with the implanted pacing system

Treatment of Atrial Fibrillation

- Ablate and pace showed improved quality of life compared with other rate control options
- Ablation of AV node and implant of a VVIR pacemaker*
  - EF increase from 32% to 42%
  - Patients with mitral valve regurgitation showed a tendency to have increased regurgitation with RV pacing

*Shis-Huang Lee, MD, et al, Am Col Card, 1998



Ablate and Pace

In the setting of chronic atrial fibrillation, the goal is to control the ventricular rate. Attempts at converting the patient's rhythm to sinus or an atrial paced rhythm have been abandoned.

In patients whose ventricular response cannot be controlled by pharmacologic therapy, more and more physicians are turning to RF (Catheter) ablation of the AV node and implantation of a VVIR pacemaker. In a multiplicity of studies, this being data from only one of those studies, hemodynamic function has improved as has quality of life and symptoms of CHF.

The downside of AV node ablation, it is inducing one disease to treat another but this disease, unlike a drug, is not reversible.

Treatment of Atrial Fibrillation

- **Summary: Control of Ventricular heart rate**
  - **Drugs**
    - Inhibit conduction through AV node
      - Beta Blockers
      - Calcium Channel Blockers
      - Digoxin
  - **Ablation**
    - AV nodal modification
    - AV nodal ablation with pacemaker implantation

Treatment of Atrial Fibrillation

- Categories of treatment
  - **Rhythm**
    - Regaining and maintaining normal heart rhythm
    - Prevention of HF and embolism
  - **Rate**
    - Control of ventricular heart rate
    - Prevent symptoms, HF and dysfunction
  - **Prevention of clotting and stroke**
    - Oral anticoagulation
    - Left atrial appendage occluding devices
    - Left atrial appendectomy at time of open heart surgery

Treatment of Atrial Fibrillation

- Prevention of clotting and stroke
  - During atrial fibrillation the atria lose their organized pumping action and fibrillate (quiver)
    - The atria don't contract during atrial fibrillation
    - Blood can pool and become stagnant creating a site for blood clot formation

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Treatment of Atrial Fibrillation

- Drugs are the treatment of choice for prevention of clotting and stroke
  - Left atrial appendage occlusion devices are still under study
- Drugs are effective; however, they don't eliminate the risk and have potentially serious complications
- Two drug categories are used:
  - Anticoagulant
  - Antiplatelet

Treatment of Atrial Fibrillation

- Anticoagulant
  - Warfarin (Coumadin)
  - Dose is very individualized
    - Must be monitored by a blood test (INR)
      - INR stands for the International Normalized Ratio
        - Therapeutic range is usually between 2.0 and 3.0 for prevention of stroke

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Treatment of Atrial Fibrillation

- Antiplatelet
  - Decreases the stickiness of circulating platelets
  - Platelets are the small blood cells that initiate the normal clotting process
    - Clopidogrel (Plavix) – VERY EXPENSIVE
      - Compromised effectiveness when used with PPI (proton pump inhibitors) such as Zantac and Prilosec
    - Aspirin
      - Much safer than Coumadin (less likely to cause abdominal bleeding)
      - Research has shown that aspirin may not be as effective as Coumadin in preventing blood clots and, therefore, strokes

Treatment of Atrial Fibrillation

- Summary
  - Prevention of clotting and stroke
    - Drug Therapy
      - Anticoagulant / Antiplatelet
  - Required therapy that remains difficult to manage with potential risks
  - Left atrial appendage occluding devices may eliminate the need for anticoagulation
    - Appropriate large scale studies are still pending

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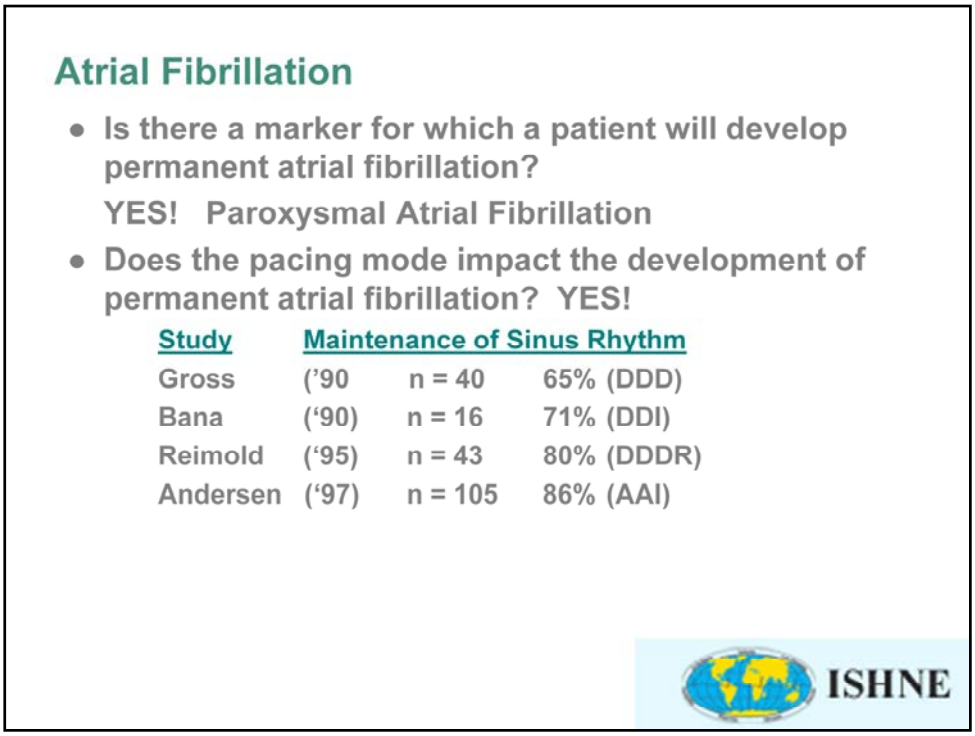

Markers for chronic atrial fibrillation

In the early days of DDD pacing (early 1980's) prior to AMS capability, the development of atrial fibrillation was initially considered a contraindication to DDD pacing. Studies were developed to identify markers for chronic atrial fibrillation, which, if present, would be a contraindication to DDD pacing. The major marker for chronic atrial fibrillation was paroxysmal atrial fibrillation prior to the implant. Amazingly, atrial based pacing (DDD or AAI) was associated with a marked reduction in the incidence of atrial fibrillation or maintenance of an organized atrial rhythm (sinus or atrial paced).

This suggested that even though paroxysmal atrial fibrillation was a marker for those patients who were most likely to develop chronic atrial fibrillation, atrial based pacing at standard rates had a beneficial effect with regard to stabilizing the atrial rhythm in 65% to 85% of the patients.

Except for the Andersen study, all the rest were retrospective and not randomized. Nonetheless, if a high risk group (PAF patients) appeared to stabilize with atrial based pacing as did patients who had sinus node dysfunction (prior slide).


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Rosario, Argentina
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