Atrial Fibrillation and Sleep Apnea

Farhat S. Khairallah, MD, FHRS, FACC
“The art of medicine consists in amusing the patient while nature cures the disease.”

—Voltaire
Classification of AF

• Paroxysmal AF is characterized by self-terminating episodes that generally last <7 days (most <24 hours),

• Persistent AF generally lasts >7 days and often requires electrical or pharmacologic cardioversion.

• Permanent AF is classified when it has failed cardioversion or when further attempts to terminate the arrhythmia are deemed futile.

# AF Definition

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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| Paroxysmal AF               | • AF that terminates spontaneously or with intervention within 7 d of onset.  
                                • Episodes may recur with variable frequency.                                                                                       |
| Persistent AF               | • Continuous AF that is sustained >7 d.                                                                                                                                                          |
| Long-standing persistent AF | • Continuous AF >12 mo in duration.                                                                                                                                                             |
| Permanent AF                | • The term “permanent AF” is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm.  
                                • Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF.  
                                • Acceptance of AF may change as symptoms, efficacy of therapeutic interventions, and patient and clinician preferences evolve.       |
| Nonvalvular AF              | • AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.                          |
Atrial Fibrillation

Mechanisms

Multiple Wavelet Reentry

Focal

(Moe G. Arch Int Pharmacodyn Ther 140:183, 1962)

Need for “Second Factor”
Atrial Electrical Remodeling

Obesity
“Second Factor”?
Effects of Obesity

- Increased Pericardial Fat
- Inflammation and increased production of pro-inflammatory cytokines
- Increased oxidative stress
- Autonomic dysfunction
Pericardial Fat

Cardiac structural changes
1) Structural and electrical remodelling.
2) Fibrosis and fatty infiltration
3) Diastolic dysfunction

Paracrine secretion of pro-inflammatory cytokines: IL-1β, TNFα

Autonomic nervous system modulation
↓ ARP
↑ activity autonomic ganglia

Atrial Fibrillation
Increased Pericardial Fat

Journal of the American College of Cardiology, 2015-07-07, Volume 66, Issue 1, Pages 1-11
Biophysical Journal 95(9) 4469–4480
Pericardial Fat
Inflammation
Oxidative Stress

Circulation. 2013;128:1748-1757
Autonomic Dysfunction

Arq. Bras. Cardiol., ahead of print  Epub Nov 03, 2015
Autonomic Nervous System

Autonomic AF - Differentiation

- Adrenergic AF
  - Tachycardia
  - Post-operative
  - Alcohol
  - Exercise
  - Emotional stress
  - Polyuria
  - Better with beta-blockers
  - More common with heart disease

- Cholinergic AF
  - Male predominance
  - Age at onset 40-50
  - Bradycardia
  - Vomiting
  - Severe constipation
  - After large meal
  - Cold carbonated beverages
  - Rest
  - Coughing
  - Diving into cold water
  - Valsalva
  - Exacerbated by digoxin, beta-blockers
  - More common without heart disease
**Figure Legend:**

Anatomic Location of the 4 GPs

Schematic posterior view of the left and right atria. The 5 major left atrial autonomic GP and axons (superior left GP, inferior left GP, anterior right GP, inferior right GP, and ligament of Marshall) are shown in yellow, whereas the coronary sinus and the vein and ligament of Marshall are shown in blue, which travels from the coronary sinus to the region between the left superior PV and the left atrial appendage. GP = ganglionated plexi; IVC = inferior vena cava; LIPV = left inferior pulmonary vein; LSPV = left superior pulmonary vein; RIPV = right inferior pulmonary vein; RSPV = right superior pulmonary vein.
From: Autonomic Denervation Added to Pulmonary Vein Isolation for Paroxysmal Atrial Fibrillation: A Randomized Clinical Trial


Figure Legend:
Anatomic Ablation of the Superior Left and Anterior Right GP
After pulmonary vein isolation, the ablation lesions are expanded to cover the anatomic site of presumed ganglionated plexi (GP) clusters. LSGP = left superior ganglionated plexi; RAGP = right anterior ganglionated plexi.
From: Autonomic Denervation Added to Pulmonary Vein Isolation for Paroxysmal Atrial Fibrillation: A Randomized Clinical Trial


Figure Legend:
Anatomic Ablation of the Inferior Left and Right GP
After pulmonary vein isolation, the ablation lesions are expanded to cover the anatomic site of presumed GP clusters. ILGP = inferior left ganglionated plexi; IRGP = inferior right ganglionated plexi.
Atrial Fibrillation or Other Sustained Atrial Arrhythmia Recurrence Across the 3 Different Ablation Strategies
Kaplan-Meier estimates were used to calculate the 2-year event rates and comparison was performed using the log-rank test stratified by study site. A 3-month blanking period after the ablation procedure was adopted. GP = ganglionated plexi; PVI = pulmonary vein isolation.
Obesity Association with AF
BMI ≥ 25

WHO Data 2010
BMI ≥ 30

WHO Data 2010
Prevalence of AF

Circulation. 2014;129:837-847
AF: BMI Effect

Men

Women

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Obesity and P Wave/PR duration

Obesity (Silver Spring). Author manuscript; available in PMC 2013 July 01
Electrophysiological Effects
Obesity results in progressive atrial structural and electrical remodeling: Implications for atrial fibrillation

Hany S. Abed MBBS, B Pharm, Chrishan S. Samuel PhD, Dennis H. Lau MBBS, PhD, Darren J. Kelly PhD, Simon G. Royce PhD, Muayad Alasady MBChB, Rajiv Mahajan MD, Pawel Kuklik PhD, Yuan Zhang MD, PhD, Anthony G. Brooks PhD, Adam J. Nelson MBBS, Stephen G. Worthley MBBS, PhD, Walter P. Abhayaratna MBBS, PhD, Jonathan M. Kalman MBBS, PhD, Gary A. Wittert MBChB, MD and Prashanthan Sanders MBBS, PhD, FHRSA

Heart Rhythm, 2013-01-01, Volume 10, Issue 1, Pages 90-100, Copyright © 2013
Electrical Remodeling

- Decrease in Conduction Velocity
- Increase in heterogeneity
- Increase burden of AF
Profibrotic Markers

- ET Receptors
- TGF-B, PDGF, CTGF,
Endothelin

A

\[ \text{ET}_A \]

\[ \text{ET}_B \]

\[ \text{ET}_C \]

B

BASELINE
OVERWEIGHT
OBESE

\[ P=0.001 \]

\[ P=0.004 \]

\[ P=0.007 \]
Structural Remodeling

- Distorted myocyte
- Wider interstitium
- Collagen deposition
## Structural Remodeling

### Table

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<td><strong>LAP (mmHg)</strong></td>
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<td>(3.7-4.9)</td>
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<td>(6.7-9.6)</td>
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Obesity and OSA
Acute Effects
Chronic Effects

Human Data

[Image of a 3D representation of atrial regions with color-coded conduction velocities and bar graphs showing conduction velocity comparisons between Reference and OSA in the right and left atrial regions, with statistical significance indicated by asterisks and hash marks.]
CPAP Use

<table>
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<tr>
<th>Study</th>
<th>Year</th>
<th>RR (95% CI)</th>
<th>Treatment</th>
<th>Control</th>
<th>Weight</th>
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<td>Kanaga et al</td>
<td>2003</td>
<td>0.51 (0.26, 1.02)</td>
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<td>Jongnarangsin et al</td>
<td>2008</td>
<td>0.70 (0.40, 1.24)</td>
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<td>Patel et al</td>
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<tr>
<td>Fein et al</td>
<td>2013</td>
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<td>19/30</td>
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<td>Karsus et al</td>
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<td>0.58 (0.37, 0.91)</td>
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<td>Nielan et al</td>
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<td>Overall (I-squared = 0.0%, p = 0.919)</td>
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<td>186/557</td>
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CPAP use: PVI vs. Non PVI

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<tr>
<td>Bazan et al</td>
<td>0.66 (0.33, 1.34)</td>
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<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.611)</td>
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<td>Post PVI</td>
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<tr>
<td>Patel et al</td>
<td>0.61 (0.51, 0.73)</td>
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<tr>
<td>Fein et al</td>
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<td>Naruse et al</td>
<td>0.58 (0.37, 0.91)</td>
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<td>Neilan et al</td>
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<td>Overall (I-squared = 0.0%, p = 0.919)</td>
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Long-term effects of catheter ablation for lone atrial fibrillation: Progressive atrial electroanatomic substrate remodeling despite successful ablation

Andrew W. Teh MBBS, Peter M. Kistler MBBS, PhD, Geoffrey Lee MBChB, Caroline Medi BMed, Patrick M. Heck BM, BCh, MD, Steven J. Spence ACCT, Joseph B. Morton MBBS, PhD, Prashanthan Sanders MBBS, PhD and Jonathan M. Kalman MBBS, PhD

Heart Rhythm, 2012-04-01, Volume 9, Issue 4, Pages 473-480, Copyright © 2012 Heart Rhythm Society
Voltage Comparison

A: Mean Voltage

B: Percentage Low Voltage
Electroanatomic Conduction

A  Percentage Complex Signals

B  Effective Refractory Periods

CS Conduction Time

SOUTHERN MEDICAL GROUP, P.A.
Can the substrate be reversed?
Effect of Weight Reduction and Cardiometabolic Risk Factor Management on Symptom Burden and Severity in Patients With Atrial Fibrillation

A Randomized Clinical Trial
Waist Circumference

A  Waist circumference

B  BMI

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| Follow-up, mo   | 75       | 75           |
| 3               | 75       | 75           |
| 6               | 72       | 75           |
| 9               | 61       | 73           |
| 12              | 52       | 57           |
| 15              | 39       | 42           |
AFSS

A  Symptom burden score

B  Symptom severity score

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<th>Controls</th>
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Lifestyle Modifications
Risk Factor Management

**Weight Management and Exercise**
- Education for permanent lifestyle change
- Life style journal
- High protein, low GI, calorie-controlled meal plan
- 30 minutes 3-4 times weekly
- Type of activity and duration

**Hyperlipidemia**
- Life style measures
  - At 3 months LDL > 100 mg/dl - start statin
  - Add Fibrate if TG > 200mg/dl
  - Start Fibrate if TG > 500mg/dl

**Glucose Tolerance**
- Glucose tolerance test
- Lifestyle measures
- HbA1c > 6.5 at 3 months – start Metformin
- Referred to a diabetes clinic

**Hypertension**
- Measure BP 2-3 times daily, No added salt diet
- Aim of <130/80mmHg at rest and <200/100 at peak exercise

**Sleep Apnea**
- Formal overnight sleep study
- AHI≥30/hour – CPAP
- Use Log in diary

**Tobacco and alcohol use**
- Smoking cessation
- Alcohol abstinence or reduction to ≤30g/week
From: Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY)


Patient Selection

Flow diagram demonstrating patient recruitment and attrition. AF = atrial fibrillation; AV = aortic valve; BMI = body mass index; Dx = diagnosis; WF = weight fluctuation; WG = weight gain; WL = weight loss.

Figure Legend:
Figure Legend:
Atrial Fibrillation Freedom Outcome According to Group

(A) Kaplan-Meier curve for AF-free survival without the use of rhythm control strategies. (B) Kaplan-Meier curve for AF-free survival for total AF-free survival (multiple ablation procedures with and without drugs). Abbreviations as in Figure 1.
From: Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-Term Follow-Up Study (LEGACY)


Outcomes of Atrial Fibrillation Freedom According to Weight Trend and Weight Fluctuation

(A) Kaplan-Meier curve for total AF-free survival (multiple ablation procedures with and without drugs) according to weight trend.

(B) Kaplan-Meier curve for total AF-free survival (multiple ablation procedures with and without drugs) according to weight fluctuation. Abbreviations as in Figure 1.

**Figure Legend:**

**Outcomes of Atrial Fibrillation Freedom According to Weight Trend and Weight Fluctuation**

(A) Kaplan-Meier curve for total AF-free survival (multiple ablation procedures with and without drugs) according to weight trend.

(B) Kaplan-Meier curve for total AF-free survival (multiple ablation procedures with and without drugs) according to weight fluctuation. Abbreviations as in Figure 1.

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Weight Management and Atrial Fibrillation

(Left) Obesity is associated with a variety of associated comorbidities. These are all associated with progression of the atrial substrate and the development of atrial fibrillation (AF). (Top) A dedicated weight management program with weight loss (WL) is associated with reverse remodeling of the atrial substrate and a dose-dependent reduction in the AF burden, which is sustained in the long term. (Bottom) The consequence of weight fluctuation, which somewhat curtails the beneficial effects of WL.

Figure Legend:
Patient Selection

Flow diagram of patient recruitment and attrition. Of 165 patients (69 in the risk factor [RF] management group and 96 in the control group), 16 were excluded from the analysis due to lack of regular follow-up in 13 from other states (7 RF management and 6 control) or systemic illness in 3 (1 with malignancy and 2 with systemic inflammatory diseases). AF = atrial fibrillation; BMI = body mass index.
From: Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation: The ARREST-AF Cohort Study


Burden of AF

Changes in AF burden according to scores on the Atrial Fibrillation Severity Scale (AFSS) questionnaire at baseline and at final follow-up. Error bars indicate 95% confidence intervals. RFM = risk factor management; other abbreviation as in Figure 1.
From: Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation: The ARREST-AF Cohort Study


Outcomes of AF Ablation

Figure Legend:

Kaplan-Meier curves for single-procedure, drug-free, AF-free survival (left) and for total AF-free survival (multiple procedures ± drugs) (right). Curves for 2 years are provided, after which <20% of patients completed follow-up. Note that data are provided after the last procedure using a 3-month blanking period. RFM = risk factor management; other abbreviation as in Figure 1.
Impact of Risk Factor and Weight Management on AF Ablation Outcomes

The schematic demonstrates the natural progression of the atrial fibrillation (AF) substrate and its impact on the maintenance of sinus rhythm (blue). Risk factor management has been demonstrated to reduce the burden of AF and also improve the outcomes of catheter ablation (salmon).
Risk Factors and Potential Lifestyle Modifications to Reduce AF

- **Alcohol Consumption**
  - Limit Alcohol Consumption to < 2 drinks/day

- **Obesity**
  - Weight Loss > 10% Body Weight

- **Diabetes Mellitus**
  - Blood Glucose Control – HbA1c < 7.0

- **Obstructive Sleep Apnea**
  - Continuous Positive Airway Pressure Utilization

- **Hypertension**
  - Maintain SBP < 140 mmHg but > 110 mmHg
Familial AF: Framingham Study

20-yr Cohort Study of 2243 Offspring Free of AF

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<th>Maternal AF</th>
<th>Paternal AF</th>
<th>One or Both Parents</th>
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<td>Entire Cohort</td>
<td>2.23</td>
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<td>1.85</td>
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<td>3.17</td>
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OR adjusted for age, sex, DM, HTN, clinically overt heart disease

Swedish Registry
Case-Cohort Study of 300,586 residents with AF/Afl

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<tbody>
<tr>
<td>Single Parent</td>
<td>1.95 (1.89-2.00)</td>
</tr>
<tr>
<td>Both Parents</td>
<td>3.87 (3.51-4.27)</td>
</tr>
<tr>
<td>Single Sibling</td>
<td>2.78 (2.69-2.87)</td>
</tr>
<tr>
<td>≥ 2 Siblings</td>
<td>5.72 (5.28-6.19)</td>
</tr>
<tr>
<td>Spouse</td>
<td>1.16 (1.13-1.19)</td>
</tr>
</tbody>
</table>
Culprit Genes for AF

Where are the genes that regulate weight? or Diabetes? or sleep apnea?

KCNQ1, KCNE1, KCNE2, KCNE3, KCNE4, KCNE5, KCND3, KCNH2, KCNA5, ABCC9

SCN10a, SCN5a, SCN1B, SCN2B, SCN3B

K+ Channels

Na+ Channels

Regulators

Grem2, Nppa

Transcription Factors

Gata2, Gata4, Pitx2, Zfhx3

Gap junction

Gja1, Gja5

Structural

Cav1, Syn2

Current Genomics, 2015, 16, 75-81
Managing AF: Importance of Symptoms

- Strategy Trial
- < 70% Rhythm control patients in sinus rhythm

AFFIRM, Circ. 2004: 109;1509.
Management of Symptoms: Manifestations

Atrial Fibrillation

- None
- Vague
- ↓ Exercise Tolerance
- Palpitations
- Frank CHF

Symptoms may be related to rate and/or irregularity.

The spectrum of symptoms may exist within the same patient.

Patients may present with no or vague symptoms and following restoration of SR, recurrent AF may cause more profound symptoms.
In Persistent AF, antiarrhythmic drugs have a 30% success at 1 year. Dofetilide is a possible exception.

FDA-Approved Rx for PAF

Radio Frequency

\[ \Delta = 48\%, \ p < 0.001 \]

9 months

16%

Cryoballoon

\[ \Delta = 62\%, \ p < 0.001 \]

9 months

69%

Durable Pulmonary Vein Isolation Critical to Success
Meta-analysis: Ablation vs AAD

Khan, Circ Arrhyth EP, 2014
Meta-analysis: First-Line Rx with Ablation

Hakalahti, Europace, 2015
Santangeli, Circ Arrhyth EP, 2015

**Pooled Data n=578**

<table>
<thead>
<tr>
<th></th>
<th>Catheter Ablation</th>
<th>AAD Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freedom from AF/AT</td>
<td>67%</td>
<td>48%</td>
</tr>
<tr>
<td>Complications</td>
<td>12.9%</td>
<td>15.6%</td>
</tr>
</tbody>
</table>

PAF 96%, age 44-58, 34 institutions, mean F/U 17 months
Factors for Safe and Successful Ablation

- Santangeli, Circ Arrhyth EP, 2015
- Chen, Europace, 2015

Bar chart showing number of pts free from AF at 12 months/1000 ablated.

- CPVA, circumferential PV ablation
- PVI, PV isolation

Pooled No PV Isolation
- Krittayapong et al. 2003
- Stabile et al. 2005
- Pappone et al. 2006
- Wazni et al. 2005
- Jais et al. 2008
- Pooled PV Isolation

50 more pts free from AF at 12 mos with PV Isolation

Bar chart showing complication rate (%).

- Low-volume <100/year: 8.5%
- Medium-volume 100–299/year: 4.9%
- High volume ≥300/year: 1.6%
Results Have Improved with Technology Advances

Proportion of patients free of AF

Contact Force Information

Log Rank Test P=0.04

Time (Days)

Freedom from AF (1 year)

Moltrasio, Di Giovanni, Di Giovanni, Chierchia, Metzner, Furnkranz, Aytemir, Anyana

Risk Factor Modification and Ablation

ARREST- AF

Consec. patients undergoing 1st ablation for AF n=281

BMI ≥ 27 and 1 CRF n=165

Refused RFM n=96

Aggressive RFM n=66
Face-to-face wt. loss Goal ≤ 10% or BMI ≤25
Ex: 90’—200’/wk

41% of referred patients did not qualify for RFM
Only 23% of all patients willing to participate.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Control</th>
<th>RFM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second Procedure</td>
<td>52%</td>
<td>46%</td>
</tr>
<tr>
<td>Third Procedure</td>
<td>15%</td>
<td>10%</td>
</tr>
</tbody>
</table>
Intensive Risk Factor Modification

LEGACY Study

Patients with AF
n=1415

BMI ≥ 27
n=825

Enrolled targeted RFM program
n=355

Terciles of weight change
Type of weight change

PermAF Complex Dz Prior Ablation, etc Refusal

Use of ablation same in all groups.
Majority of patients received rhythm control.

Despite intensive program, only 37% could achieve target weight loss (9% of screened patients).

Pathak, JACC, 2014
Fitness and Need for AF Intervention

CARDIO-FIT: 308 patients assessed for therapy success as function of baseline fitness and gain post structured fitness program.

No data on use of drugs or ablation.

1415 screened, 827 with BMI ≥27, 308 (22%) examined.

Only 25% (78) were in top cohort (5.5% of all subjects).

49% (152) did poorly despite intensive program.

Pathak, JACC, 2015
How Does Risk Factor Modification Work in the Majority of AF Patients?
“AF is a final common electrical diagnosis for multiple different primary diseases”

- Dr. Robert Kowal