Appreciating Diverse Pathogenesis of Atrial Remodeling for Atrial Fibrillation Prevention and Management

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Progression of Atrial Fibrillation
Progression of Atrial Fibrillation

Paroxysmal Atrial Fibrillation
AF that terminate spontaneously or with intervention within 7 days
Progression of Atrial Fibrillation

Paroxysmal Atrial Fibrillation
AF that terminate spontaneously or with intervention within 7 days

Persistent Atrial Fibrillation
Continuous AF that last more than 7 days and do not self-terminate
Progression of Atrial Fibrillation

Paroxysmal Atrial Fibrillation
AF that terminate spontaneously or with intervention within 7 days

Persistent Atrial Fibrillation
Continuous AF that last more than 7 days and do not self-terminate

Permanent Atrial Fibrillation
The term is used when the patient and clinician make a decision to stop further attempts to restore sinus rhythm
## Baseline Characteristics of Patients

- 171 patients with Paroxysmal AF
- Follow up period (yr) \( 14.1 \pm 8.1 \)
- Male / Female \( 125 / 46 \)
- Left atrial dimension (mm) \( 40.6 \pm 7.7 \)
- Fractional shortening (%) \( 35.7 \pm 8.7 \)
- History of heart failure 35 (20.5%)
Progression of Paroxysmal AF into Chronic Form

Progression of Paroxysmal AF into Chronic Form

- 5.5% / year

Meta-analysis of 19 cohort studies

Atrial Fibrillation is a Progressive Disease

\[
\begin{align*}
\tau^2 &= 0.0177 \\
I^2 &= 97.58\% \\
\text{Pseudo } R^2 &= 47.96\%
\end{align*}
\]

Diversity of AF Clinical Course

mean 8.0 ± 6.0 years

Number of patients

Time required for progression to chronic AF (years)
69-year-old patient with paroxysmal ‘lone’ AF

(A) 7-day-ECG in a 69-year-old patient with paroxysmal ‘lone’ atrial fibrillation. The patient had a history of paroxysmal atrial fibrillation of 22 years with frequent episodes per week or even per day (asterisks), however, the individual episodes stayed short within minutes or maximally few hours with no evidence for progression.

(B) During sinus rhythm, this patient presented with frequent premature atrial complexes with ‘P-on-T’ phenomenon (black asterisks) and also frequent atrial salvoes (white asterisks).

Another 69-year-old patient with paroxysmal ‘lone’ AF

(C) 7-day-ECG in another 69-year-old patient with paroxysmal ‘lone’ atrial fibrillation. This patient had a short history of atrial fibrillation of only 6 months, however, he presented with atrial fibrillation episodes lasting already >48 h in the initial 7-day-ECG (arrows). Hardly any premature atrial complexes were found during periods of sinus rhythm (not shown).

(D) This patient progressed to persistent atrial fibrillation within only another 3 months.

STAR AF II

Limitation of Catheter Ablation for Persistent AF

P = 0.15 for the overall comparison, by the log-rank test

Freedom from Atrial Fibrillation (%)

Months since First Ablation

Conceptual Framework of AF Initiation, Maintenance and Progression

Atrial Remodeling

Diversity of Etiological Factors for AF

- Smoking
- Alcohol
- Hypertension
  - Hypertrophic cardiomyopathy
- Valvular disease
  - LV systolic dysfunction
  - LV diastolic dysfunction
- Congenital heart disease
- Coronary artery disease
  - WPW syndrome
- Man
- Athlete
- Atrial Fibrillation
- Diabetes
- Age
- Obesity
- Sleep apnea syndrome
- Chronic kidney disease
- Thyroid dysfunction
- Inflammation
Diversity of Etiological Factors for AF

- Diabetes
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- LV diastolic dysfunction
- Congenital heart disease
- Coronary artery disease
- WPW syndrome
- Chronic kidney disease
- Inflammation
- Sleep apnea syndrome
- Obesity
- Smoking
- Age
- Man
- Athlete
Vulnerability to Atrial Arrhythmia in Diabetic Rat

GK: Goto-Kakizaki rat (diabetic rat)
RAR: repetitive atrial response

Electrophysiological Property of Diabetic Atria

- **max RAR (beats)**
  - Wistar: 0
  - GK: 70
  - P < 0.01

- **Atrial ERP (ms)**
  - Wistar: 30
  - GK: 40
  - n.s.

- **Intra-atrial Activation Time (ms)**
  - Wistar: 12
  - GK: 18
  - P < 0.01

Enhanced Fibrosis in Diabetic Rat Atrium

Expression of RAGE in Diabetic Rat Atrium

RAGE = Receptor for Advanced Glycation Endproducts (AGEs)
OPB = OPB-9195 (Inhibitor of AGEs formation)

* P<0.01 vs control

Diabetes Enhances CTGF Expression in the Atrium

CTGF = Connective Tissue Growth Factor
OPB = OPB-9195 (Inhibitor of AGEs formation)
* P<0.01 vs control, † P<0.01 vs DM

Inhibition of AGEs Formation Prevents Atrial Fibrosis

OPB = OPB-9195 (Inhibitor of AGEs formation)

* P<0.01 vs control, † P<0.01 vs DM

Mechanism of Diabetes-related AF

Protein or Lipid → Hyperglycemia Oxidative Stress → AGEs → RAGE

- Atrial fibrosis
- Atrial conduction disturbance

CTGF

Origin of Fibroblasts during Fibrosis

Figure 2

Endothelial-mesenchymal Transition in Human AF

Endothelial-mesenchymal Transition in Human AF

Diversity of Etiological Factors for AF

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- Smoking
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- Man
- Athlete
- Diabetes
- Thyroid dysfunction
- Obesity
- Sleep apnea syndrome
- Inflammation
- Chronic kidney disease
- Alcohol
- Hypertension
  - Hypertrophic cardiomyopathy
  - Valvular disease
    - LV systolic dysfunction
    - LV diastolic dysfunction
    - Congenital heart disease
  - Coronary artery disease
    - WPW syndrome
Long-term Obstructive Sleep Apnea Model Rat

<table>
<thead>
<tr>
<th>Group</th>
<th>Ventilator Settings</th>
<th>Intubation</th>
<th>Extubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham group</td>
<td></td>
<td>Intubation</td>
<td>Extubation</td>
</tr>
<tr>
<td>Open group</td>
<td></td>
<td></td>
<td>Intubation</td>
</tr>
<tr>
<td>OSA group</td>
<td></td>
<td></td>
<td>Extubation</td>
</tr>
</tbody>
</table>

Ventilator settings:
- Volume control
- Tidal volume: 2.5 ml
- Respiratory rate: 72/min
- FiO₂ 0.21 (room air)
- Isoflurane 2%

Long-term Obstructive Sleep Apnea Model Rat

A

Open

Sinus rhythm
25 Hz 3 sec burst

B

OSA

Atrial Fibrillation
25 Hz 3 sec burst

C

AF duration (sec)

D

AF inducibility

E

AF inducibility during acute OSA

Long-term Obstructive Sleep Apnea Model Rat

Long-term Obstructive Sleep Apnea Model Rat

A

Sham

Open

OSA

B

t-Cx43 Expression

Relative Expression

Sham (n=6)  Open (n=5)  OSA (n=5)

* p<0.05; *** p<0.001 vs. Sham  ### p<0.001 vs. Sham

C

t-Cx43 Lateralization

Lateralization Ratio

Sham (n=6)  Open (n=5)  OSA (n=5)

# Results of Previous Studies on Connexins in AF (Animal Models)

<table>
<thead>
<tr>
<th>Species</th>
<th>AF Type/Animal Model</th>
<th>Cx40 Protein</th>
<th>Cx43 protein</th>
<th>Remarks</th>
<th>Author</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Dog</td>
<td>exp. NA</td>
<td>hetero NA</td>
<td>exp. NA dephos. NA</td>
<td>Elvan</td>
<td>1997</td>
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<tr>
<td>2</td>
<td>Goat</td>
<td>exp. →</td>
<td>hetero ↑</td>
<td>exp. → dephos. →</td>
<td>Van der Velden</td>
<td>1998</td>
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<tr>
<td>3</td>
<td>Goat</td>
<td>exp. ↓</td>
<td>hetero ↑</td>
<td>exp. → dephos. ↑</td>
<td>Van der Velden</td>
<td>2000</td>
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<tr>
<td>4</td>
<td>Rabbit</td>
<td>exp. ↓</td>
<td>hetero NA</td>
<td>exp. ↓ dephos. NA</td>
<td>Haugan</td>
<td>2006</td>
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<td>5</td>
<td>Dog</td>
<td>exp. ↓</td>
<td>hetero ↑</td>
<td>exp. ↓ dephos. ↑</td>
<td>Ryu</td>
<td>2007</td>
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<td>6</td>
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<td>exp. → dephos. NA</td>
<td>Sawaya</td>
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<td>7</td>
<td>Dog</td>
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<td>exp. → dephos. ↑</td>
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<td>2009</td>
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<td>8</td>
<td>Rat</td>
<td>exp. →</td>
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<td>exp. NA dephos. NA</td>
<td>Hayano</td>
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<td>9</td>
<td>Rat</td>
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<td>Cx43 transfer prevented AF</td>
<td>Reil</td>
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<td>10</td>
<td>Pig</td>
<td>NA NA</td>
<td>exp. ↓ dephos. →</td>
<td>Cx43 transfer prevented AF</td>
<td>Bikou</td>
<td>2011</td>
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<tr>
<td>11</td>
<td>Rabbit</td>
<td>exp. ↓</td>
<td>hetero ↑</td>
<td>exp. ↑ dephos. ↑</td>
<td>Xiao</td>
<td>2011</td>
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<tr>
<td>12</td>
<td>Rat</td>
<td>exp. ↓</td>
<td>hetero NA</td>
<td>exp. NA dephos. NA</td>
<td>Kim</td>
<td>2011</td>
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</table>

### Results of Previous Studies on Connexins in AF (Human Studies)

<table>
<thead>
<tr>
<th>Species</th>
<th>AF Type/Animal Model</th>
<th>Cx40 Protein</th>
<th>Cx43 Protein</th>
<th>Remarks</th>
<th>Author</th>
<th>Year</th>
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<tbody>
<tr>
<td>13</td>
<td>Human Post-operative AF (CAD)</td>
<td>↑</td>
<td>→</td>
<td>→</td>
<td>Dupont²³</td>
<td>2001</td>
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<tr>
<td>14</td>
<td>Human Chronic AF &gt;1 y</td>
<td>↑</td>
<td>NA</td>
<td>→</td>
<td>Polontchouk²⁴</td>
<td>2001</td>
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<tr>
<td>15</td>
<td>Human Chronic AF &gt;1 y</td>
<td>↓</td>
<td>↑</td>
<td>→</td>
<td>Kostin²⁵</td>
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<tr>
<td>16</td>
<td>Human Chronic AF &gt;5 mo</td>
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<td>↑</td>
<td>→</td>
<td>Nao²⁶</td>
<td>2003</td>
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<tr>
<td>17</td>
<td>Human Chronic AF &gt;6 mo</td>
<td>→↓</td>
<td>↑</td>
<td>→</td>
<td>Kanagaramatnam²⁷</td>
<td>2004</td>
</tr>
<tr>
<td>18</td>
<td>Human Lone AF and AF with MVD</td>
<td>↑</td>
<td>NA</td>
<td>↑</td>
<td>Wetzel²⁸</td>
<td>2005</td>
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<tr>
<td>19</td>
<td>Human Persistent AF &gt;3 mo</td>
<td>↓</td>
<td>↓</td>
<td>→</td>
<td>Wilhelm²⁹</td>
<td>2006</td>
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<tr>
<td>20</td>
<td>Human Chronic AF &gt;3 mo</td>
<td>→</td>
<td>→</td>
<td>→</td>
<td>Takeuchi³⁰</td>
<td>2006</td>
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<tr>
<td>21</td>
<td>Human Chronic AF up to 6 mo</td>
<td>↓</td>
<td>NA</td>
<td>↑</td>
<td>Rucker-Martin³¹</td>
<td>2006</td>
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<tr>
<td>22</td>
<td>Human Chronic AF &gt;1 y (valve disease)</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>Dhein³²</td>
<td>2008</td>
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<td>23</td>
<td>Human Post-operative AF (CAD)</td>
<td>→</td>
<td>NA</td>
<td>→</td>
<td>Li³³</td>
<td>2009</td>
</tr>
<tr>
<td>24</td>
<td>Human Persistent AF (MVD, CAD)</td>
<td>→</td>
<td>NA</td>
<td>→</td>
<td>Girmatsion³⁴</td>
<td>2009</td>
</tr>
<tr>
<td>25</td>
<td>Human Permanent AF &gt;3 mo</td>
<td>→</td>
<td>NA</td>
<td>↑</td>
<td>Adam³⁵</td>
<td>2010</td>
</tr>
</tbody>
</table>

Abbreviations: ATP, atrial tachypacing; CAD, coronary artery disease; dephos, dephosphorylation; exp, expression; hetero, heterogeneity; SR, sinus rhythm; MVD, mitral valve disease; NA, not available.
Diversity of Etiological Factors for AF

- Alcohol
- Hypertension
- Hypertrophic cardiomyopathy
- Valvular disease
  - LV systolic dysfunction
  - LV diastolic dysfunction
- Congenital heart disease
- Coronary artery disease
  - WPW syndrome
- Chronic kidney disease

- Atrial Fibrillation

- Smoking
- Age
- Man
- Athlete
- Diabetes
- Thyroid dysfunction
- Obesity
- Sleep apnea syndrome
- Inflammation
Modifiable Etiological Factors for AF

- Smoking
- Alcohol
- Hypertension
- Hypertrophic cardiomyopathy
- Valvular disease
- LV systolic dysfunction
- LV diastolic dysfunction
- Man
- Age
- Athlete
- Diabetes
- Thyroid dysfunction
- Obesity
- Sleep apnea syndrome
- Inflammation
- Chronic kidney disease
- Coronary artery disease
- WPW syndrome
### TABLE 2 Risk Factor, Echocardiographic, and AF Severity Changes

<table>
<thead>
<tr>
<th></th>
<th>Control Group (n = 88)</th>
<th></th>
<th></th>
<th>RFM Group (n = 61)</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-Up‡</td>
<td>p Value*</td>
<td>Baseline</td>
<td>Follow-Up‡</td>
<td>p Value*</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>96.6 ± 16.8</td>
<td>95.8 ± 17.6</td>
<td>0.13</td>
<td>100.7 ± 17.6</td>
<td>87.5 ± 14.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>32.1 ± 4.7</td>
<td>31.8 ± 4.9</td>
<td>0.12</td>
<td>33.5 ± 4.6</td>
<td>29.1 ± 3.9</td>
<td>&lt;0.001</td>
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<tr>
<td>Mean SBP, mm Hg</td>
<td>158.7 ± 21.3</td>
<td>138.2 ± 18.0</td>
<td>&lt;0.001</td>
<td>160.8 ± 20.3</td>
<td>126.8 ± 12.8</td>
<td>&lt;0.001</td>
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<tr>
<td>DM with HbA₁c ≥7%, n</td>
<td>17</td>
<td>5</td>
<td></td>
<td>9</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>No. with AHI &gt;30</td>
<td>54</td>
<td>46</td>
<td></td>
<td>32</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of antiarrhythmic agents</td>
<td>1.0 ± 0.2</td>
<td>0.7 ± 0.7</td>
<td>&lt;0.001</td>
<td>1.1 ± 0.3</td>
<td>0.3 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No. of antihypertensive agents</td>
<td>1.6 ± 1.2</td>
<td>1.9 ± 1.3</td>
<td>0.2</td>
<td>1.5 ± 1.1</td>
<td>1.2 ± 0.9</td>
<td>0.04</td>
</tr>
</tbody>
</table>
The ARREST-AF Cohort Study

Aggressive Risk Management Improved Long-term Success of AF Ablation

Summary

- Atrial fibrillation (AF) progresses with the development of atrial arrhythmogenic substrate (Atrial Remodeling).

- Our long-term clinical observation of AF patients showed wide variety of time spent in paroxysmal AF, suggesting the diverse pathogenesis of AF.

- Recent experimental studies also demonstrated the diversity of atrial remodeling according to the underlying conditions.
Future Directions in AF Treatment

One-size-fits-all Approach
Disease treatment and prevention strategies are developed for the average person, with less consideration for the differences between individuals.

Precision Medicine
An emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.