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Atrial remodelling in permanent atrial fibrillation. Mechanism and implications

Norbert Jost, PhD

Department of Pharmacology & Pharmacotherapy, University of Szeged; Division for Cardiovascular Pharmacology, Hungarian Academy of Sciences, Szeged, Hungary

3rd International Conference on Clinical and Experimental Cardiology
April 15-17, 2013, Hilton Chicago/Northbrook
When the pulse strikes out in long beats and smoothly for a long time and then the beats of the pulse become smaller and hard on their own account, then a quick death will occur and no cure can be effected.

*Huang Ti Nei Ching Su Wen, China ~ 2000 B.C.*
Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. It can occur at any age but becomes extremely common in the elderly, with a prevalence approaching 20% in patients 85 years of age. AF is characterized by disorganized, high-rate (300-500/min) atrial electrical activity and it is associated with shorter action potential duration (APD) and effective refractory period and a loss of rate-dependent APD adaptation that involve concomitant alterations in ion current activity.
General schema representing AF mechanisms and the role of remodeling
Principal mechanisms that can produce AF. Reentry involves a vulnerable substrate, which requires a trigger for reentry initiation. Ischemia, inflammation, and dilation make atria more vulnerable to AF. AF that results from any mechanism causes tachycardia-induced remodeling. Even if AF is initially maintained by ectopic activity or single-circuit reentry in a given patient, ATR-induced spatially heterogeneous refractoriness abbreviation creates conditions favorable to multiple-circuit reentry, which may then become the AF-maintaining mechanism. Thus, multiple circuit reentry may be a final common pathway AF mechanism in many patients.
Principal mechanisms that can produce AF – *the reentry.*

**Fundamental determinants of reentry**

- Circuit time: has to be greater than RP.
- Favored by:
  - Short refractory periods
  - Slow conduction
  - Long pathways available

WL (Wavelength) = ERP x conduction velocity (*Allesie’s WL theory*).

The main condition for maintaining of the AF is that WL to be smaller than the circuit time.

**How remodeling promotes reentry**

- Normal atrial size
- Increased circuit path-space
- Impaired connexin function
- Tissue fibrosis
- Decreased source current ($I_{Na}$)
- Slowed conduction
- Normal conduction
- Decreased inward current ($Ca^{2+}$)
- Increased outward current ($K^+$)

**Shortened refractory periods**

- Normal atrial size
- Increased circuit path-space
- Impaired connexin function
- Tissue fibrosis
- Decreased source current ($I_{Na}$)
- Slowed conduction
- Normal conduction
- Decreased inward current ($Ca^{2+}$)
- Increased outward current ($K^+$)
The role of pulmonary veins

- The muscular sleeves of the pulmonary veins contain in large amount (40%) myocytes able for spontaneous diastolic depolarization (ectopic foci).
- The originating atrial systoles are the triggers of AFs. They can be suppressed by ablation.
- There were often observed spontaneous DADs or catecholamine induced EADs.
- This PV-automaticity may be a therapeutically relevant observation.
Atrial Fibrillation Begets Atrial Fibrillation
A Study in Awake Chronically Instrumented Goats

Maurits C.E.F. Wijffels, MD; Charles J.H.J. Kirchhof, MD, PhD;
Rick Dorland, BS; Maurits A. Allessie, MD, PhD
Atrial fibrillation remodelling

AF is a progressive disease (paroxysmal → persistent → permanent)
(all changes, which are involved to initiate and maintain the AF)

1. Electrical remodelling
2. Contractile remodelling
3. Structural remodelling

Tachycardia (ATR)

Congestive heart failure

Sarcolemmal ion channels
Signal transduction and „working” proteins
Gap-junctions, ECM
Neurohormonal systems,
Autonomic nervous system (RAAS)
eetc.

Circulus vitiosus, which promote the initiation, renewal, stabilization and maintaining of the AF

The legendary hydra of Hercules
Lloyd and Langberg (J Cardiv Electrophysiol, 2006; 17: 236)
AF - electrical remodelling

<table>
<thead>
<tr>
<th>Current</th>
<th>Main subunit (protein)</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>$I_{Na}$</td>
<td>$\rightarrow$ Nav1.5</td>
<td>$\leftrightarrow$ SCN5A</td>
</tr>
<tr>
<td>$I_{Cal}$</td>
<td>$40-60% \downarrow \alpha_{1C}$</td>
<td>$40-60% \downarrow$ CACNA1C</td>
</tr>
<tr>
<td>$I_{to}$</td>
<td>$40-50% \downarrow$ Kv4.3</td>
<td>$30-60% \downarrow$ KCND3</td>
</tr>
<tr>
<td>$I_{Kur}$</td>
<td>$50-60% \downarrow$ Kv1.5</td>
<td>$\leftrightarrow$ KCNA5</td>
</tr>
<tr>
<td>$I_{Kr}$</td>
<td>$\leftrightarrow$ HERG</td>
<td>$\leftrightarrow$ KCNH2</td>
</tr>
<tr>
<td>$I_{Ks}$</td>
<td>n.a. KvLQT1</td>
<td>$70-80% \uparrow$ KCNQ1</td>
</tr>
<tr>
<td>$I_{K1}$</td>
<td>$100-140% \uparrow$ Kir2.1-2.3</td>
<td>$100% \uparrow$ KCNJ2/12/4</td>
</tr>
<tr>
<td>$I_{KACCh}$</td>
<td>$50% \downarrow$ GIRK1/4</td>
<td>$50% \downarrow$ KCNJ3/5</td>
</tr>
<tr>
<td>n.a. $I_{K(ATP)}$</td>
<td>n.a. Kir6.2</td>
<td>$35% \downarrow$ KCNJ11</td>
</tr>
<tr>
<td>n.a. $I_{NCX}$</td>
<td>n.a. NCX1</td>
<td>$60-70% \uparrow$ NCX1</td>
</tr>
</tbody>
</table>
AF - electrical remodelling, transient outward current ($I_{to}$)

Recordings of $I_{to}$ obtained with the voltage protocol shown in the inset at 0.1 Hz in representative cells obtained from a sham-operated dog (A) and dogs subjected to 1 (B), 7 (C), and 42 (D) days of rapid atrial pacing.
AF - electrical remodelling, L-type calcium current ($I_{CaL}$)
AF - electrical remodelling, inward rectifier potassium current ($I_{K1}$)

The G Protein–Gated Potassium Current $I_{K,ACh}$ Is Constitutively Active in Patients With Chronic Atrial Fibrillation

D. Dobre, MD; A. Friedrich, CandMed; N. Voigt, CandMed; N. Jost, PhD; E. Wettwer, PhD; T. Christ, MD; M. Knaut, MD; U. Ravens, MD

**A**

<table>
<thead>
<tr>
<th>Basal current $I_{K,ACh}$ (CCh, 2 μM)</th>
<th>Basal current $I_{K,ACh}$ (CCh, 2 μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR</td>
<td>cAF</td>
</tr>
<tr>
<td>$V_m$ (mV)</td>
<td>$V_m$ (mV)</td>
</tr>
<tr>
<td>-100 to +40 mV</td>
<td>-100 to +40 mV</td>
</tr>
<tr>
<td>0.5 Hz, RT</td>
<td>500 ms</td>
</tr>
<tr>
<td>500 ms</td>
<td>+40 mV</td>
</tr>
<tr>
<td>50 mV</td>
<td>-50 mV</td>
</tr>
<tr>
<td>40 mV</td>
<td>-80 mV</td>
</tr>
<tr>
<td>20 mV</td>
<td>-100 mV</td>
</tr>
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**A**

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<thead>
<tr>
<th>Basal current $I_{K,ACh}$ (CCh, 2 μM)</th>
<th>Basal current $I_{K,ACh}$ (CCh, 2 μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>S2</td>
</tr>
<tr>
<td>CCh, 2 μM</td>
<td>CCh, 2 μM</td>
</tr>
<tr>
<td>8 pA/pF</td>
<td>4 pA/pF</td>
</tr>
<tr>
<td>60 s</td>
<td>60 s</td>
</tr>
<tr>
<td>Tertiapin, 10 nM</td>
<td>Tertiapin, 10 nM</td>
</tr>
<tr>
<td>$V_m$ = -100 mV</td>
<td>$V_m$ = -100 mV</td>
</tr>
</tbody>
</table>

**A**

**D**

<table>
<thead>
<tr>
<th>Control</th>
<th>After tertiapin (10 nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SR</td>
<td>AF</td>
</tr>
<tr>
<td>24/8</td>
<td>16/5</td>
</tr>
</tbody>
</table>

**E**

<table>
<thead>
<tr>
<th>Log[Tertiapin] (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
</tbody>
</table>

*Circulation. 2005;112:3697-3706.*
AF - electrical remodelling, ultrarapid delayed rectifier potassium current ($I_{Kur}$)

Wettwer et al Circulation, 110:2299-2306

$I_{Kur}$ blockade in treating cAF?
The loss of contractile force of the myocardium, mainly due to $I_{\text{CaL}}$ reduction (as a protective mechanism against Ca$^{2+}$ overload) and consequently by the damage of the Ca$^{2+}$-homeostasis. Hipocontractility will increase the wall stretch, and thereby, causes atrial dilation (LAV $\uparrow$). *Electrical and contractile remodelling go hand in hand***!!!
Structural remodelling (ASR)

A paradigm shift in treatment of atrial fibrillation: from electrical to structural therapy? (Heidbüchel, Eur Heart J, 2003; 24:2077-2078)

The importance of upstream/non channel treatment of AF!!

The structural remodelling is the main cause for the progrident behaviour of the AF (paroxysmal → persistent → permanent). In long lasting AF the following “low flow ischaemia” -type structural changes occur:

- increase in cell size
- perinuclear accumulation of glycogen
- central loss of sarcomeres (myolysis)
- alterations in connexin expression (gap-junctions)
- changes in mitochondrial shape
- fragmentation of sarcoplasmic reticulum
- homogeneous distribution of nuclear chromatin
- changes in quantity and localization of structural cellular proteins
- fibrosis!!!
Cardiomyocytes in normal myocardial tissue are electrically coupled primarily in an end-to-end fashion by intercellular gap-junctional complexes. Reactive fibrosis results in extracellular matrix expansion between bundles of myocytes while reparative fibrosis replaces degenerating myocytes. Both patterns of collagen distribution become exaggerated during structural remodeling.
Structural remodelling of atrial myocytes after 4 months of AF in the goat 2.

Connexins

Labeling of Cx40 (green) and Cx43 (red) revealed a clear reduction in Cx40 and no change in Cx43 expression

Ultrastructure during AF the atrial nuclei get a more homogeneous distribution of chromatin. For comparison the normal clustering of chromatin at the nuclear membrane is indicated by arrows in the upper left panel. During AF many small donut shaped mitochondria can be found (arrowheads right lower panel)

The positive feedback correlation between the three types of atrial remodellings

Electrical and contractile remodelling may occur in minutes, hours and days – reversible after conversion

Structural remodelling develops within 3-4 months, and is hardly or even nonreversible

Therapeutic implications

Therapeutic consequences of ATR

- To develop atria-selective antiarrhythmic drugs
- Repolarization lengthening - \( I_{Kr} \) blockade
- \( I_{CaL} \) blockade – to prevent \( Ca^{2+} \)-overload
- \( I_{CaT} \) blockade – mibefradil
- \( I_{Kur} \) blockade (\( I_{Kur} + I_{Kr} \)?)
- \( I_{K1} \) blockade (?)
- \( I_{K,ACH} \) blockade (NIP-142, NIP-151)
- Amiodarone

Therapeutic consequences of ASR

- Drugs to prevent against fibrosis
- „Gap-junction therapy”- rotigaptide (GAP-486)
- Nonselective stretch-sensitive cation channels blockers
Thank you for your attention!!

Department of Pharmacology & Pharmacotherapy, University of Szeged; Szeged, Hungary
Profibrotic factors

- Angiotensin II (presence of fibrosis in transgenic ACE overexpressed mice; Xiao et al, Am J. Physiol, 2004; 165: 1019-1032)
- Transforming growth factor-β1 (TGF-β1) (in spite of normal structural heart an increased atrial conduction heterogeneity and AF prevalence was observed in TGF-β1 overexpressed mice; Verheule et al, Circ Res; 94:1458-1465)
- Platelet-derived growth factor
- Connective tissue growth factor
- Oxidative stress
- Inflammation
Recent hemorrhagic micro-infarcts and extensive replacement fibrosis

Extensive replacement fibrosis (scarring) in the inferior part of the terminal crest

Mechanism by which CHF leads to AF (in turn, AF causes changes that can impair cardiac function, leading to potentially deleterious positive feedback systems)
Mechanisms underlying ATR. Rapid atrial rates increase potentially cytotoxic Ca$^{2+}$ loading. Autoprotective $I_{CaL}$ reductions occur via rapidly developing functional changes ($I_{CaL}$ inactivation) and more slowly developing changes in gene and protein expression. Decreased $I_{CaL}$ reduces Ca$^{2+}$ loading but decreases APD. Diminished APD shortens refractoriness and reduces the wavelength (WL), which allows for smaller and more atrial reentry circuits, thus making AF unlikely to terminate. Atrial tachycardia also increases inward-rectifier currents such as $I_{K1}$ and $I_{KAcH}$, which further reduces APD and promotes AF.
Fetal phenotype dedifferentiation of the atrial myocardium by a clear increase in fetal α-smooth muscle actin (red staining in upper pictures). In the lower pictures of this panel the myocytes are stained for desmin (red). The nuclei are stained by blue DAPI. During AF desmin loses its cross-striated pattern in the cytoplasm and at the intercalated disks the intensified desmin staining is no longer present.

Ausma et al. Circulation 1997; 96:3157-3163
The role of pulmonary veins

The pulmonary veins (PV) may be sources of ectopic beats, which may cause paroxismal AF.

Angiogram of a left inferior pulmonary vein depicting the source and exit of actopic activity

Thanks' for your kind attention!!!!!!!
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